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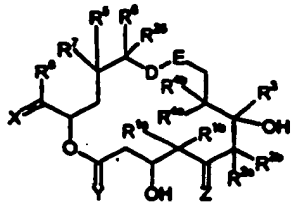
54) Title: EPOTHILONE DERIVATIVES, THEIR PREPARATION PROCESS, INTERMEDIATE PRODUCTS AND THEIR PHARMACEUTICAL USE

57) Abstract

The invention relates to new epothilon derivatives of general formula (I) where the substituents Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, D–E, R^5, R^6, R^{25}, R^7, R^8 et X have the meaning given in the description. These new compounds co-operate with tubulin by stabilising formed microtubuli. They are able to affect cell splitting in a phase-specific way and are useful for the treatment of malignant tumours, such as ovarian, stomach, colon, lung, head or neck cancer, adenocarcinoma, malignant melanoma and acute lymphoid and myeloid leukaemia. They are also adapted to anti-angiogenesis therapy and to treatment of chronic inflammation diseases (psoriasis, arthritis). These new compounds can be applied on polymer materials or introduced therein to avoid uncontrolled proliferation on medical implants and to improve tolerance of these medical implants. The inventive compounds can be used alone or in combination with other ingredients or classes of substances which can be used in tumour therapy to obtain respectively additional actions or synergistic effects.



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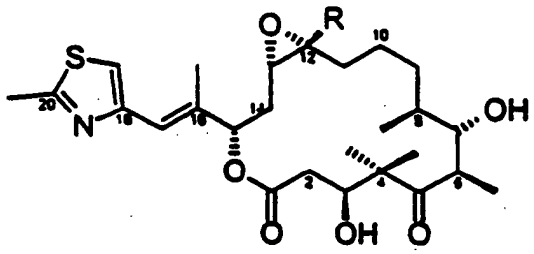
Epothilone Derivatives, Their Preparation Process, Intermediate Products and Their Pharmaceutical Use

The cytotoxic effect of the natural substance epothilone A (R = hydrogen) and epothilone B (R = methyl)



epothilone A (R = H), epothilone B (R = CH_3)

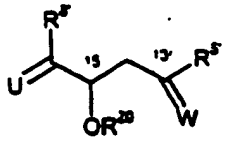
is described by Höfle et al., for example, in Angew. Chem. 1996, 108, 1671-1673. Due to the in-vitro selectivity to breast- and intestinal cell lines, and due to the fact that they have a significantly higher activity in comparison to taxol against P-glycoprotein-forming, multiresistant tumor lines, as well as because of the physical properties which are improved in comparison to taxol, for example, a solubility in water which is 30 times higher, this novel class of structures is of special interest for the development of a drug for the therapy of malignant tumors.

The natural substances are not sufficiently stable, either chemically or metabolically, for development of a drug. In order to eliminate these disadvantages, modifications are necessary in the natural substance. Such modifications are possible only by total synthesis and require synthesis strategies which make it possible to produce broad modifications in the natural substance. The goal of the structural changes is also to increase the therapeutic spectrum. This can be done by improvement of the selectivity of action and/or by reduction of undesirable toxic side effects and/or by increasing the activity.

The total synthesis of epothilone A was described by Schinzer et al. in Chem. Eur. J. 1996, 2, No. 11, 1477-1482 and in Angew. Chem. 1997, 109, No. 5, p. 543-544).

Epothilone derivatives were already described by Höfle et al., in WO 97/19086. These derivatives were prepared starting from natural epothilone A or B.

Another synthesis of epothilone and epothilone derivatives was described by Nicolaou et al., in Angew. Chem. 1997, 109, No. 1/2, p. 170-172. The synthesis of epothilones A and B and of some epothilone analogs was published in Nature, Volume 387, 1997, p. 268-272. The synthesis of epothilone A and its derivatives [was published?] in J. Am. Chem. Soc., Volume 119, No. 34, 1997, p. 7960-7973, as well as the Synthesis of Epothilone A and B and some epothilone ...



C

where

$R^{5'}$, $R^{8'}$ have the meaning already given in general formula I for R^5 and R^8 and

R^{20} is a hydrogen atom or a protecting group PG^5

U an oxygen atom, two alkoxy groups OR^9, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^{10} or a group $CR^{11}R^{12}$, where

R^9 stands for a C_1-C_{20} alkyl group,

R^{10} stands for hydrogen or a protective group PG^6,

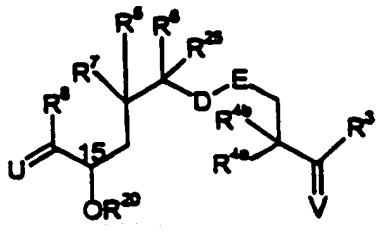
R^{11}, R^{12} are the same or different and stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^{11} and R^{12} together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring

W is an oxygen atom, two alkoxy groups OR^{21}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, or H/OR^{22}, where

R^{21} stands for a C_1-C_{20} alkyl group,

R^{22} stands for hydrogen or a protecting group PG^7.

15. Intermediate products having general formula BC

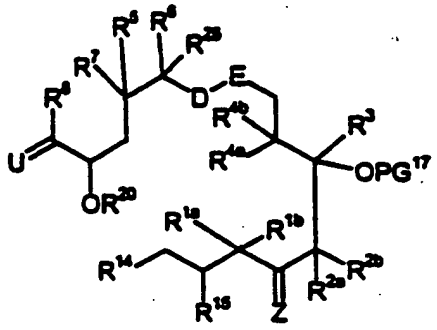


BC,

where

R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^{20}, D, E, U and V have the meaning already given.

16. Intermediate products having general formula ABC



ABC,

where R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^8, R^{14}, R^{15}, D, E, U and Z have the meaning already given.

17. Pharmaceutical preparations, containing at least one compound having general formula I according to Claim 1, as well as a pharmaceutically compatible carrier.

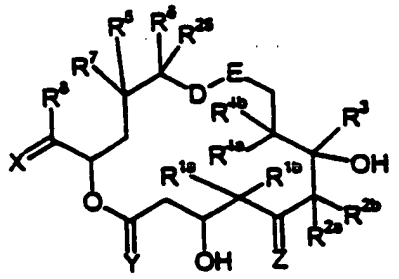
18. Application of the compounds having general formula I according to Claim 1, for the production of drugs.

{German page 4 seems like a continuation of German page 1 - T.]
analogs are described in J. Am. Chem. Soc., Volume 119, No. 34, 1997, p. 7974-7991, also by Nicolaou et al.

Nicolaou et al., also described in Angew. Chem. 1997, 109, No. 19, p. 2181-2187 the preparation of epothilone A analogs with combinatorial solid-phase synthesis. Some epothilone B analogs are also described there.

The task of the present invention consists in making available new epothilone derivatives, which are sufficiently stable both chemically and metabolically for drug development and which are superior to the natural derivatives with regard to their therapeutic spectrum, their selectivity of action and/or adverse toxic side effects and/or their strength of activity.

The present invention describes the new epothilone derivatives having general formula I,



I,

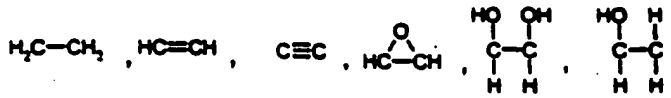
where

R^{1a}, R^{1b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_m$ group with m = 2, 3, 4, or 5,

R^{2a}, R^{2b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_n$ group with n = 2, 3, 4 or 5,

R^3 stands for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^{4a}, R^{4b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_p$ group with p = 2, 3, 4 or 5,

D-E stands for  groups,

R^5 stands for C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^6, R^7 each stand for a hydrogen atom, together for an additional bond, or an oxygen atom,

R^{25} stands for hydrogen, C_1-C_{10} alkyl, where the alkyl group can optionally be substituted by one or several halogen atoms and/or hydroxyl groups,

R^8 stands for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, all of which can be substituted,

X is an oxygen atom, two alkoxy groups OR^9, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^{10} or a group $CR^{11}R^{12}$, where

- R^9 stands for a C_1-C_{20} alkyl group,
- R^{10} stands for hydrogen or a protecting group PG^1,
- R^{11}, R^{12} are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group, or R^{11} and R^{12} together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

Y stands for an oxygen atom or two hydrogen atoms,

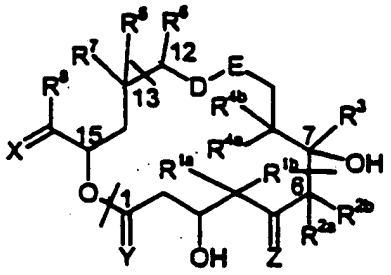
Z is an oxygen atom or H/OR^{13},

where

- R^{13} is hydrogen or a protecting group PG^2,

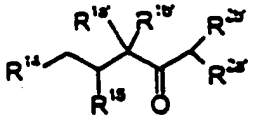
including all stereoisomers from these compounds, and also their mixtures.

The preparation of the new epothilone derivatives is based on linking three fragments, A, B and C, and is done analogously to that already described for epothilone A and epothilone B derivatives (that is, instead of R^5, only a hydrogen atom can be there) in WO 99/07692. The interfaces are as shown in general formula I'



I'

A means a C1-C6 fragment (epothilone numbering) of the general formula



A,

where

$R^{1a'}$, $R^{1b'}$, $R^{2a'}$ and $R^{2b'}$ have the meanings already given for R^{1a}, R^{1b}, R^{2a} and R^{2b}, and

R^{14} is CH_2OR^{14a}, CH_2-Hal, CHO, CO_2R^{14b}, COHal,

R^{15} is hydrogen, OR^{15a}, Hal, OSO_2R^{15b},

R^{14a}, R^{15a} are hydrogen, SO_2 alkyl, SO_2 aryl, SO_2 aralkyl or together can stand for the $-(CH_2)_o$ group or together for a $CR^{16a}R^{16b}$ group,

R^{14b}, R^{15b} are hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,

R^{16a}, R^{16b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20}-aralkyl, or together for a $-(CH_2)_q$ group,

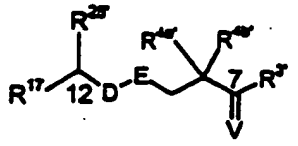
Hal is halogen,

o is 2 to 4,

q is 3 to 6,

including all stereoisomers as well as their mixtures, as well as the free hydroxyl groups in R^{14} and R^{15} can be etherified or esterified, the free carbonyl groups in A and R^{14} can be ketalized, converted into an enol ether or reduced, as well as the free acid groups in A can be converted into their salts with bases.

B stands for a C7-C12 fragment (epothilone numbering) having the general formula



B

where

$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and R^{25} have the meanings already given for R^3, R^{4a}, R^{4b} and R^{25}, and

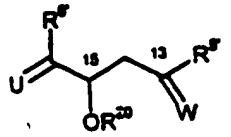
R^{17} stands for a hydroxyl group, halogen, a protected hydroxyl group OPG^3, a phosphonium halide group $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphin-oxide group $P(O)Ph_2$ (Ph = phenyl),

V stands for an oxygen atom, two alkoxy groups OR^{18}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, or H/OR^{19},

R^{18} is C_1-C_{20} alkyl,

R^{19} is hydrogen or a protecting group PG^4.

C stands for a C13-C16 fragment (epothilone numbering) having general formula



C

where

$R^{5'}$, $R^{8'}$ have the meaning already given in general formula I for R^5 and R^8, and

R^{20} is a hydrogen atom or a protecting group PG^5,

U is an oxygen atom, two alkoxy groups OR^9, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^{10} or a $CR^{11}R^{12}$ group, where

R^9 stands for a C_1-C_{20} alkyl group,

R^{10} stands for hydrogen or a protecting group PG^6,

R^{11}, R^{12} are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, a C_7-C_{20} aralkyl group or R^{11} and R^{12} together with the

methylene carbon, stand for a 5- to 7-membered carbocyclic ring,

an oxygen atom, two alkoxy group OR^{21}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, or for H/OR^{22},

where

R^{21} is a C_1-C_{20} alkyl group,

R^{22} is hydrogen or a protecting group PG^7.

As alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^{16a}, R^{16b} and R^{25}, straight-chain or branched alkyl groups with 1-10 carbon atoms come into consideration, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, decyl.

As alkyl groups R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14b}, R^{15b} and R^{18}, straight-chain or branched alkyl groups with 1-20 carbon atoms come into consideration, for example, the groups mentioned in the previous paragraph as well as their corresponding higher homologs.

The alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14b}, R^{15b}, R^{16a}, R^{16b} and R^{18} can be perfluorinated or substituted by 1-5 halogen atoms, hydroxyl groups, C_1-C_4 alkoxy groups, C_6-C_{12} aryl groups (which may be substituted by 1-3 halogen atoms).

As aryl group, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14b}, R^{15b}, R^{16a} and R^{16b}, substituted and unsubstituted carbocyclic or heterocyclic groups with one or several hetero-atoms, for example, phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, which may be mono- or polysubstituted by halogen, OH, O-alkyl, CO_2H, CO_2 alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups, come into consideration.

The aralkyl groups in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^4, R^5, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14b}, R^{15b}, R^{16a} and R^{16b} may contain up to 14 C atoms, preferably 6 to 10 C-atoms in the ring and 1 to 8, preferably 1 to 4 atoms in the alkyl chain. As aralkyl groups, for example, benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, pyridylpropyl come

into consideration. The rings may be monosubstituted or polysubstituted by halogen, OH, O-alkyl, CO_2H, CO_2 alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups.

The alkoxy groups contained in X of general formula I should each contain 1 to 20 carbon atoms, with methoxy, ethoxy, propoxy, isopropoxy and t-butyloxy groups being preferred.

As representatives of the protective groups PG, alkyl and/or aryl substituted silyl, C_1-C_{20} alkyl, C_4-C_7 cycloalkyl, which may contain additionally an oxygen atom in the ring, aryl, C_7-C_{20} aralkyl, C_1-C_{20} acyl as well as aroyl are to be named.

As alkyl, silyl and acyl groups for the protective groups PG, the groups known to the person skilled in the art come into consideration. Preferred are the alkyl or silyl groups which can be easily cleaved from the corresponding alkyl and silyl ethers, for example, methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl groups, as well as alkylsulfonyl and arylsulfonyl groups. As acyl groups, for example, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl, which may be substituted with amino and/or hydroxyl groups, come into consideration.

The acyl groups PG^1 and PG^2 in R^{10} and R^{13} contain 1 to 20 carbon atoms, but formyl, acetyl, propionyl, isopropionyl and pivalyl groups are preferred.

The index m in the alkylene group formed from R^{1a} and R^{1b} preferably stands for 2, 3 or 4.

The C_2-C_{10} alkylene-α,ω-dioxy group possible for X is preferably an ethylene ketal or neopentyl ketal group.

The group R^{25} is preferably a hydrogen atom, a methyl, ethyl, propyl, hydroxymethyl, fluoromethyl or trifluoromethyl group.

The substituents can be chosen in the compounds having general formula I in such a way that

R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^{25} and R^7 can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

R^5, R^6, R^{25}, R^7, R^8 and X all can have the meaning given in general formula I, and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^{25} and R^7 can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^5, R^6, R^{25}, R^7, R^8 and X can all have the meaning given in general formula I, and the rest of the molecule is identical with the naturally occurring epothilone A or B, or

R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^{25}, R^7, R^8 and X can all have the meaning given in general formula I, and the rest of the molecule is identical with the naturally occurring epothilone A or B.

Another variation according to the invention provides those compounds in which R^5 stands for a methyl, ethyl or propyl group, and then preferably R^6 and R^7 together form an additional bond or an epoxy group.

The compounds named below are preferred according to the invention:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9-,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14,1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,14-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5-dimethylene-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,14-trimethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8-dimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8-dimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5-trimethylene-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,14-trimethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8-trimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8-trimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-methyl-4-oxazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9,dione
and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7,14-diethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1,10-diethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1,10-diethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,-9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,14-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thizaolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-14-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13,14-hexamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12,16-hexamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12,16-hexamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

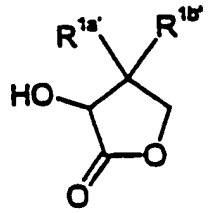
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,-13,14-hexamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,10,-12,16-hexamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(pyridyl)ethenyl)-1,8,8,-10,12,16-hexamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

Preparation of the partial fragments A (WO 99/07692)

The partial fragments (synthesis units) having general formula A can be prepared easily as starting material from

a) a pantolactone having general formula IIa



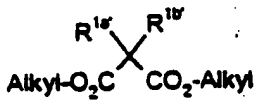
II a

where

$R^{1a'}$, $R^{1b'}$ stand for a methyl group

or

b) from a malonic acid dialkyl ester having general formula XXVIII



XXVIII

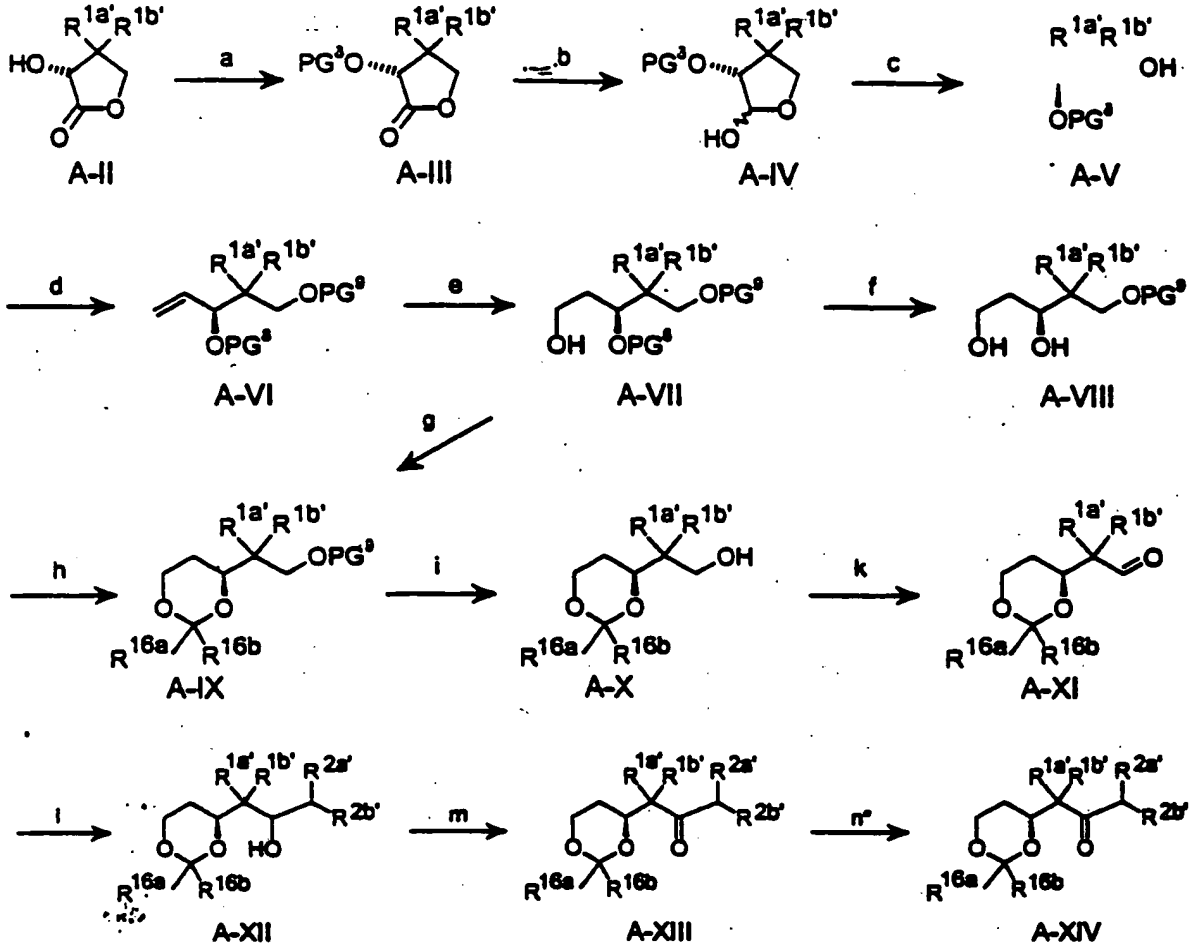
where

$R^{1a'}$, $R^{1b'}$ have the meaning given in general formula A and the alkyl groups, independently of one another, stand for a C_1-C_{20} alkyl, C_3-C_{10} cycloalkyl or C_4-C_{20} alkylcycloalkyl group.

The partial fragments A, in which $R^{1a'} = R^{1b'}$ = methyl, can be prepared from an inexpensive pantolactone in an efficient way with an optical purity of > 98% ee.

The synthesis is described in the following Scheme 1 using D-(-)-pantolactone as example. From the L-(+)-pantolactone, one obtains the corresponding ent-A-II to ent-A-XIV, which correspond to the enantiomeric compounds of A-II to A-XIV, and from racemic DL-pantolactone one obtains the corresponding racemic compounds rac-A-II to rac-A-XIV:

Scheme 1



*: only when $R^{2a'}$ or $R^{2b'}$ in A-XIII are hydrogens

Step a (A-II ➡ A-III):

The free hydroxyl group of the pantolactone (A-II) is protected according to methods known to persons skilled in the art. As protective group PG^8, the protective groups known to the person skilled in the art come into consideration, for example, methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl group.

A survey is found, for example, in "Protective Groups in Organic Synthesis", Theodora W. Green, John Wiley and Sons.

Those protective groups which can be cleaved under acidic reaction conditions are preferred, for example, the methoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl group. The tetrahydropyranyl group is especially preferred.

Step b (A-III ⇒ A-IV):
The protected lactone A-III is reduced to the lactol A-IV. As reducing agents, aluminum hydrides modified in their reactivity come into consideration, for example, diisobutylaluminum hydride. The reaction is carried out in an inert solvent, for example, toluene, preferably at low temperatures.

Step c (A-IV ⇒ A-V):
The lactol A-IV is opened with the addition of a C-atom to the hydroxyolefin A-V. The methods known to the person skilled in the art are suitable for this, for example, the olefination according to Tebbe, the Wittig- or Wittig/Horner reaction, the addition of an organometallic compound with elimination of water. The Wittig reaction is preferred, using methyltriarylphosphonium halides, for example, methyltriphenylphosphonium bromide with strong bases, for example, n-butyllithium, potassium tert-butanolate, sodium methanolate, sodium hexamethyldisilazane; n-butyllithium is preferred as base.

Step d (A-V ⇒ A-VI):
The free hydroxyl group in A-V is protected according to methods known to the person skilled in the art. As protective group PG^9, the protective groups known to the expert come into consideration as they were already named for PG^8 in step a (A-II ⇒ A-III).

Those protective groups are preferred which can be cleaved under the action of fluoride, for example, the trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl group.
The tert-butyldimethylsilyl, triisopropylsilyl and tert-butyldiphenylsilyl groups are especially preferred.

Step e (A-VI ⇒ A-VII):
Water is added to the double bond in A-VI according to anti-Markovnikov. For this purpose, the methods known to the person skilled in the art are suitable, for example, reaction with boranes, the subsequent oxidation of which leads to the corresponding boric acid esters and to their saponification. For example, the borane-tetrahydrofuran complex, the borane-dimethylsulfide complex, 9-borabicyclo[3.3.1]nonane in an inert solvent, for example, tetrahydrofuran or diethyl ether are preferred as boranes. As oxidizing agent, preferably hydrogen peroxide is used for the saponification of the boron esters, preferably alkali hydroxides, such as, for example, sodium hydroxide are used.

Step f (A-VI ⇒ A-VII):
The protective group PG^8 introduced under step a) is now cleaved according to methods known to person skilled in the art. If this is a protective group which can be cleaved with an acid, then, dilute mineral acids in aqueous-alcoholic solutions, the use of a catalytic amount of acids, for example, para-toluenesulfonic acid, para-toluenesulfonic acid-pyridinium salt, camphorsulfonic acid in alcoholic solutions, preferably in ethanol or in isopropanol, are suitable.

Step g (A-VII ⇒ A-IX):
A common protection of both alcohol functions of the monoprotected 1,3-diol in A-VII is possible by direct ketalization with a carbonyl compound having general formula R^{16a}-CO-R^{16b}, or by reketalization with a ketal having general formulas R^{16a}-$C(OC_2H_5)_2$-R^{16b}, R^{16a}-$C(OC_2H_4)_2$-R^{16b}, R^{16a}-$C(OCH_2C(CH_3)_2CH_2O)$-R^{16b} where, in each case, R^{16a} and R^{16b} have the meanings given above, using acid catalysis. As acids, the acids already named under step f) are suitable as the use of para-toluenesulfonic acid, optionally with the addition of copper(II) or cobalt(II) salts, for example, copper(II) sulfate is preferred.

Step h (A-VIII ⇒ A-IX):
A protection of both alcohol functions of the 1,3-diol in A-VIII is possible by direct ketalization with a carbonyl compound having general formula R^{16a}-CO-R^{16b}, or by reketalization with a ketal having general formulas R^{16a}-$C(OC_2H_5)_2$-R^{16b}, R^{16a}-$C(OC_2H_4)_2$-R^{16b}, R^{16a}-$C(OCH_2C(CH_3)_2CH_2O)$-R^{16b}, where in each case R^{16a} and R^{16b} have the meanings given above, using acid catalysis. Reketalization is preferred preferably with 2,2-dimethoxy-

propane. As acids, the acids already named under step f) are suitable and the use of camphorsulfonic acid is preferred.

Step i (A-IX ⇒ A-X):
The protective group PG^9 introduced in step d) is now cleaved using methods known to the person skilled in the art. If this is a silyl ether, then reaction with fluorides, for example, tetrabutylammonium fluoride, the hydrogen fluoride-pyridine complex, potassium fluoride or the use of dilute mineral acids, the use of catalytic amounts of acids, for example, para-toluenesulfonic acid, para-toluenesulfonic acid pyridinium salt, camphorsulfonic acid in alcoholic solutions, preferably in ethanol or isopropanol is suitable for cleavage.

Step k (A-X ⇒ A-XI):
The oxidation of the primary alcohol in A-X to the aldehyde is done according to methods known to the person skilled in the art. For example, let us name oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide-pyridine complex, the oxidation according to Swern or related methods, for example, using oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinan, the use of nitrogen oxides, for example, N-methylmorpholino-N-oxide in the presence of suitable catalysts, for example, tetrapropylammonium perruthenate in inert solvents. Preferably, the oxidation is carried out according to Swern as well as with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate.

Step l (A-XI ⇒ A-XII):
The reaction of the aldehyde A-XI to alcohols having formula A-XII is done with organometallic compounds having the general formula $M\text{-}CHR^{2a'}R^{2b'}$, where M stands for an alkali metal, preferably lithium, or a divalent metal MX, where X represents a halogen and the groups $R^{2a'}$ and $R^{2b'}$ each have the meanings given above. Magnesium and zinc are preferred as divalent metal and the halogen X is preferably bromine, chlorine and iodine.

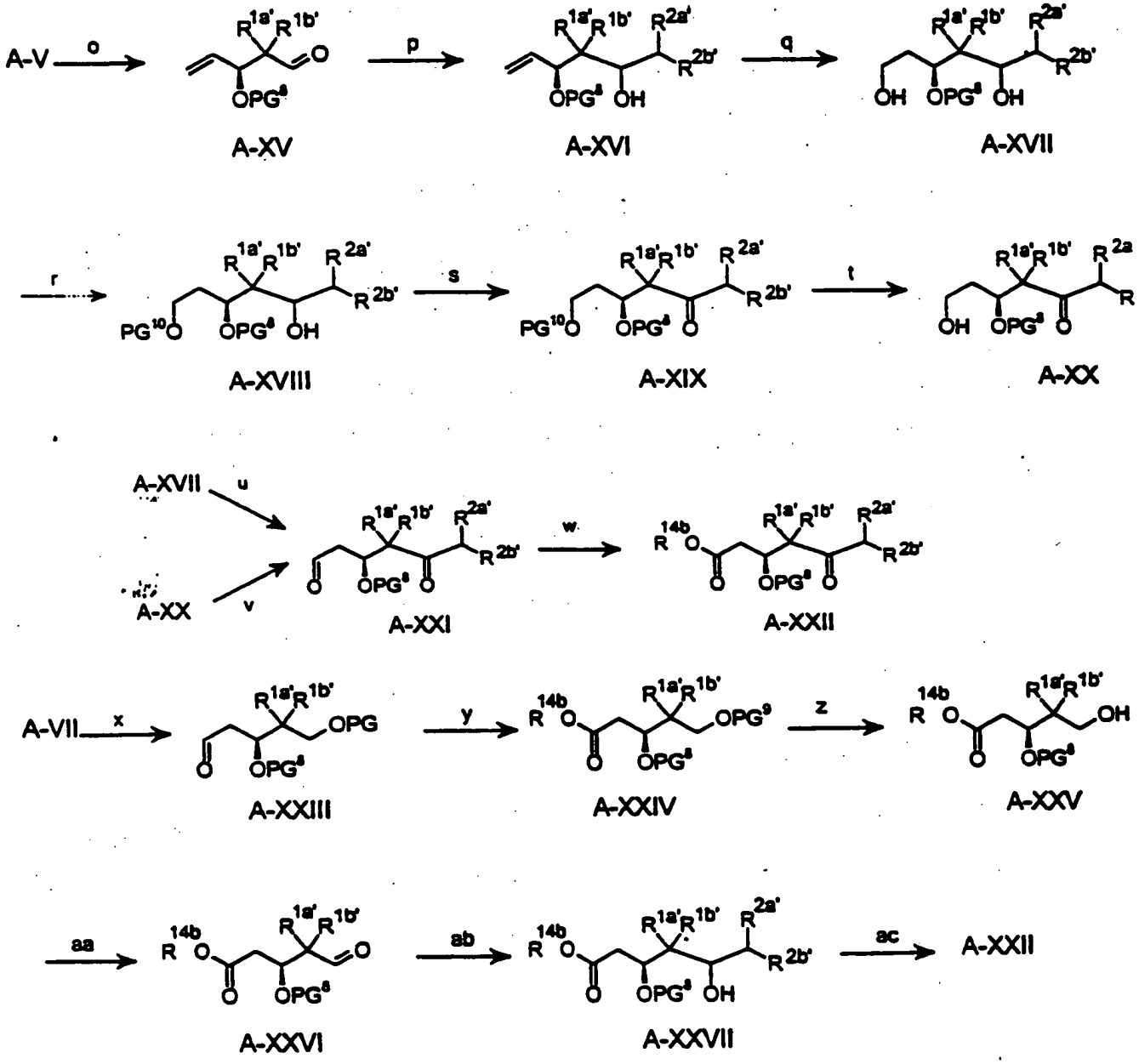
Step m (A-XII ⇒ A-XIII):
The oxidation of the secondary alcohol in A-XII-A-XIII is done under the conditions given in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step n (A-XIII ⇒ A-XIV):
For the case that $R^{2a'}$ in A-XIII is hydrogen, there is a possibility that, for this purpose, a second group $R^{2a'}$ be introduced, which has the meanings give above, except hydrogen. For this purpose, using strong bases, for example, lithium diisopropylamide, the ketone in A-XIII is converted in the enolate and reacted with a compound having general formula $X\text{-}R^{2a'}$, where X represents a halogen. The halogen X is preferably chlorine, bromine and iodine.

The method described above can also be used for the synthesis of C_1-C_6 epothilone units, which contain a carboxylic acid or its ester at C-1 (R^{14} = $-CO_2R^{14b}$ in A).

The synthesis of unit A-XXII is described in Scheme 2 below using the example of the intermediate step A-V derived from D-(-)-pantolactone. From L-(+)-pantolactone, one obtains the corresponding compounds ent A-V to ent-A-XXVII, which are enantiomeric with compounds ent-A-V to ent-A-XXVII and from racemic DL-pantolactone, the corresponding racemic compounds rac-A-V to rac-A-XXVII are obtained:

Scheme 2


A-V
o
p
q
A-XV
A-XVI
A-XVII
r
s
t
A-XVIII
A-XIX
A-XX
A-XVII
u
A-XX
v
w
A-XXI
A-XXII
A-VII
x
y
z
A-XXIII
A-XXIV
A-XXV
aa
ab
ac
A-XXVI
A-XXVII
A-XXII

Step o (A-V ⇒ A-XV):
The oxidation of the primary alcohol in A-V to the aldehyde A-XV is done under the conditions given in step k). The oxidation method according to Swern is preferred.

Step p (A-XV ⇒ (A-XVI):
The reaction of the aldehyde A-XV to alcohols having formula A-XVI is done with organometallic compounds having the general formula M-CHR$^{2a'}$R$^{2b'}$, where M stands for an alkali metal, preferably lithium, or a divalent metal MX, where X represents a halogen and the groups R$^{2a'}$ and R$^{2b'}$ each have the meanings given above. As the divalent metal, magnesium and zinc are preferred and the halogen X is preferably chlorine, bromine and iodine.

Step q (A-XVI ⇒ A-XVII):
Water is added to the double bond in A-XVI according to anti-Markovnikov. The methods described under e) are suitable for this.

Step r (A-XVII ⇒ A-XVIII):
The free hydroxyl group in A-XVII is protected according to the methods known to the person skilled in the art. As the protective group PG^{10}, the protective groups known to the person skilled in the art come into consideration as they were already named above for PG^{8} in step a (A-II ⇒ A-III).

Those protective groups are preferred which can be cleaved off under basic or hydrogenolytic reaction conditions, for example, the benzyl, para-nitrobenzyl, acetyl, propionyl, butyryl, and benzoyl group.

The benzoyl group is especially preferred.

Step s (A-XVIII ⇒ A-XIX):
The oxidation of the secondary alcohol in A-XVII to the ketone A-XIX is done under the conditions given in step k). Oxidation with N-methylmorpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step t (A-XIX ⇒ A-XX):
The protective group PG^{10} in XIX is now cleaved selectively. If it is a protective group that can be cleaved hydrogenolytically, then preferably the hydrogenation is carried out in the presence of palladium or platinum catalysts in inert solvents, for example, ethyl acetate or ethanol. If it is a protective group that can be cleaved with a base, then preferably saponification with carbonates in alcoholic solution is used, for example, with potassium carbonate in methanol, saponification with aqueous solutions of alkali hydroxides, for example, lithium hydroxide or sodium hydroxide, using organic solvents which are miscible with water, for example, methanol, ethanol, tetrahydrofuran or dioxane.

Step u) A-XVII ⇒ A-XXI):
The oxidation of the alcohols in A-XVII to the ketoaldehyde A-XXI occurs under the conditions named in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate as well as the Swern method are preferred.

Step v) A-XX ⇒ A-XXI):
The oxidation of the primary alcohol in A-XX to the ketoaldehyde A-XXI is done under the conditions given in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step w) (A-XXI ⇒ A-XXII):
The oxidation of the aldehyde in A-XXI to the carboxylic acid A-XXII (R^{14b} = hydrogen) is carried out using methods known to the person skilled in the art. For example, let us mention oxidation according to Jones, oxidation with potassium permanganate, for example, in an aqueous system consisting of tert-butanol and sodium dihydrogen phosphate, oxidation with sodium chlorite in aqueous tert-butanol, optionally in the presence of a chlorine scavenger, for example, 2-methyl-2-butene.

Oxidation of the aldehyde in A-XXI to the ester A-XXII, where R^{14b} has the meanings give above and is not hydrogen, can be carried out, for example, with pyridinium dichromate and the desired alcohol HO-R^{14b} in an inert solvent, such as dimethylformamide.

Step x (A-VII ⇒ A-XXIII):
The oxidation of the primary alcohol in A-VII to the aldehyde A-XXIII is done under the conditions given in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropyl-ammonium perruthenate as well as the Swern method are preferred.

Step y (A-XXIII ⇒ A-XXIV):
The oxidation of the aldehyde A-XXIII to the carboxylic acid or its ester A-XXIV is done under the conditions already described under w).

Step z (A-XXIV ⇒ A-XXV):
The protective group PG^9, introduced in step d) is cleaved off as described in step i.

Step aa (A-XXV ⇒ A-XXVI):
The oxidation of primary alcohol in A-XXV to the aldehyde A-XXVI is done under the conditions described in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate as well as the Swern method are preferred.

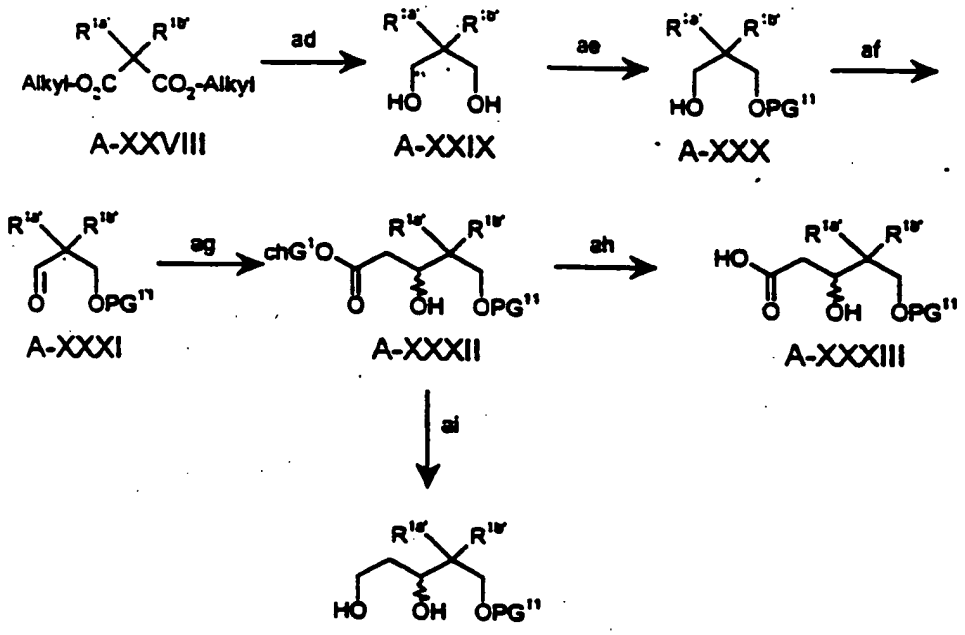
Step ab (A-XXVI ⇒ A-XXVII):
The reaction of the aldehyde A-XXVI to alcohols having the formula A-XXVII is done under the conditions described in step l).

Step ac (A-XXVII ⇒ A-XXII):
The oxidation of the secondary alcohol in A-XXVII to ketone A-XXII is done under the conditions described in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

The compounds having formula A in which $R^{1a'}$ and $R^{1b'}$ all can have the meaning given in general formula A can be prepared furthermore from inexpensive or easily accessible malonic acid dialkyl esters in an efficient way in high optical purity.

The synthesis is described in the following Scheme 3:

Scheme 3



A-VIII or ent-A-VIII

Step ad (A-XXVIII ➡ A-XXIX):
Correspondingly substituted malonic acid ester derivatives A-XXVIII, which are either commercially available or can be prepared from malonic acids or their alkyl esters according to methods known to the person skilled in the art, are reduced to diols A-XXIX. Reducing agents known to the person skilled in the art are suitable for this, for example, diisobutyl-aluminum hydride, complex metal hydride, for example, lithium aluminum hydride.

Step ae (A-XXIX ➡ A-XXX):
A free hydroxyl group in A-XXIX is protected selectively according to methods known to the person skilled in the art. As protective group PG^{11}, those protective groups known to the person skilled in the art already mentioned for PG^{8} in step a (A-II ➡ A-III) come into consideration.

Silicon-containing protective groups are preferred.

Step af (A-XXX ⇒ A-XXXI):
The oxidation of the remaining primary hydroxyl group in A-XXX to the aldehyde A-XXXI is done under the conditions given in step k). Oxidation with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate, the use of pyridinium chlorochromate, pyridinium dichromate as well as the Swern method are preferred.

Step ag (A-XXXI ⇒ A-XXXII):
The aldehyde A-XXXI are reacted with an ester of acetic acid $chG^1OC(O)CH_3$, where chG^1 stands for a chiral auxiliary group, in the sense of an aldol reaction. The compounds $chG^1OC(O)CH_3$ are used in the optically pure form in the aldol reaction. The type of chiral auxiliary group determines if the aldol reaction runs with higher diastereoselectivity or gives a diastereoisomer mixture that can be separated with physical methods. A survey on comparable diastereoselective aldol reactions is found in Angew. Chem. 99 (1987), 24-37. For example, optically pure 2-phenyl-cyclohexanol, pulegol, 2-hydroxy-1,2,2-triphenylethanol, 8-phenylmenthol are suitable as auxiliary chiral groups chG^1-OH.

Step ah (A-XXXII ⇒ A-XXXIII):
The diastereoisomerically pure compounds A-XXXII can be converted according to methods known to the person skilled in the art by saponification of the ester unit with simultaneous liberation of the reusable chiral auxiliary component chG^1-OH, into pure enantiomeric compounds of the type A-XXXIII or ent-A-XXXIII. Carbonates in alcoholic solution, for example, potassium carbonate in methanol, aqueous solutions of alkali hydroxides, such as lithium hydroxide or sodium hydroxide, are suitable for saponification with the use of organic water-miscible solvents, such as methanol, ethanol, tetrahydrofuran or dioxane.

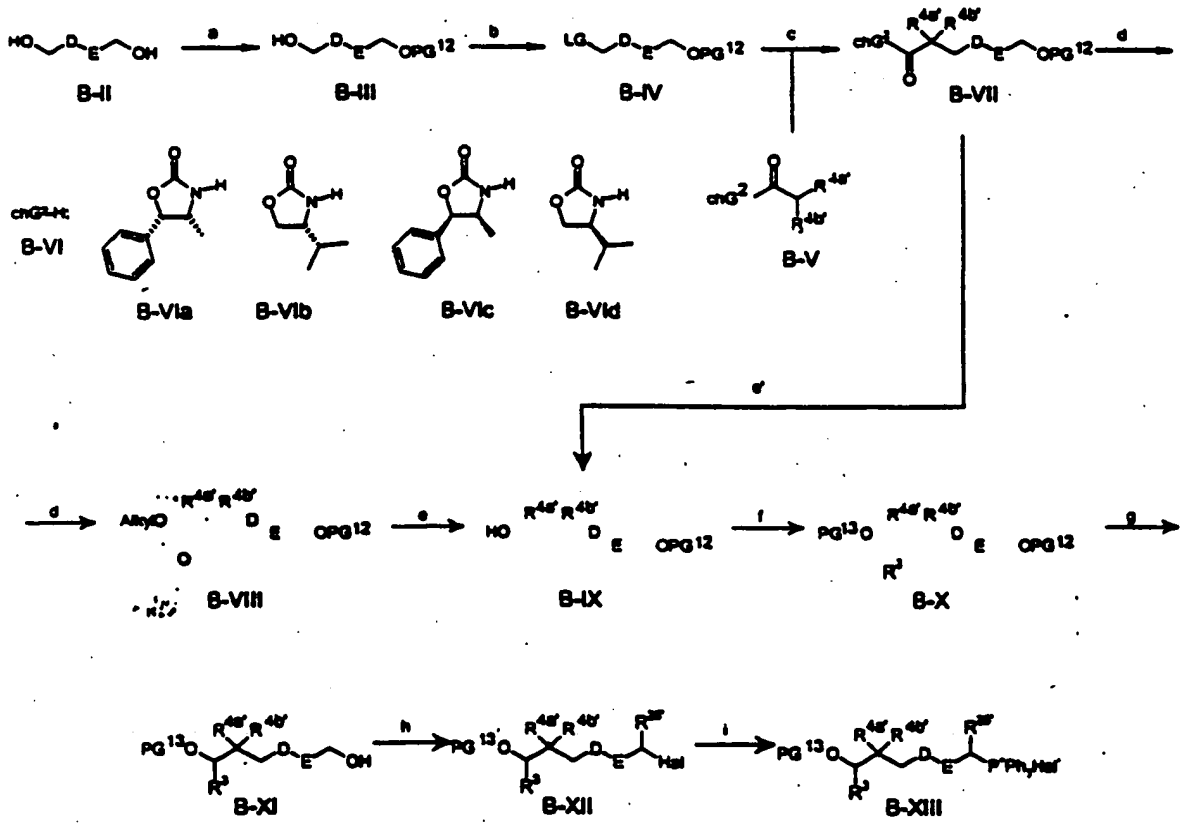
Step ai (A-XXXII ⇒ A-VIII):
Alternatively to step ah), the chiral auxiliary group can also be removed reductively. In this way, the pure enantiomeric compounds of type A-VIII or ent-A-VIII are obtained. The reduction can be carried out using methods known to the person skilled in the art. As reducing agents, for example, diisobutylaluminum hydride and complex metal hydrides, for example, lithium aluminum hydride come into consideration.

The compounds A-VIII or ent-A-VIII can be converted, as described before, into compounds of the type A-XIII or ent-A-XIII. Correspondingly, compounds of the type A-XXXIII or ent-A-XXXIII can be converted according to the method described above into compounds of the type A-XXII or ent-A-XXII.

Alternatively to the method described above, the sequence can also be carried out without the use of a chiral auxiliary group chG^1. In this way, the racemic mixtures of compounds of the type rac-A-VIII or rac-A-XXXIII are obtained through the corresponding racemic precursors. These mixtures can be separated again according to methods known to the person skilled in the art for resolution of racemates, for example, chromatography on chiral columns. However, continuation of the synthesis can also be performed with the racemic mixtures.

Preparation of partial fragment B (see also WO 99/07692)

Scheme 4



Step a (B-II ⇒ B-III):
A hydroxyl group in B-II is protected using methods known to the person skilled in the art. As protective group PG^{12}, the protective groups known to the person skilled in the art come into consideration, as already mentioned before for PG^{8} in step a (A-II ⇒ A-III).

Silicon-containing protective groups which can be cleaved under acidic reaction conditions or with the use of fluoride are preferred, for example, trimethylsilyl, triethylsilyl, tert-butyl-dimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl group.

The tert-butyldimethylsilyl group is especially preferred.

Step b (B-III ⇒ B-IV):
The free hydroxyl group in B-III is converted into a leaving group LG according to methods known to the person skilled in the art. For example, halogens, such as bromine or iodine, or alkyl or arylsulfonates, which can be prepared from the corresponding sulfonic acid halides or sulfonic acid anhydrides according to methods known to the person skilled in the art are suitable as leaving group LG.

The preferred leaving group LG is trifluoromethanesulfonate.

Step c (B-IV ⇒ B-VII):
The compound B-IV is alkylated with the enolate of a carbonyl compound having general formula B-V, where chG^{2} is a simple alkoxy group but can also be a chiral auxiliary group, using methods known to the person skilled in the art. The enolate is prepared by the action of strong bases, for example, lithium diisopropylamide, lithium hexamethyldisilazane at low temperatures. As chiral auxiliary group chG^{2}-H (B-VI), those chiral alcohols which are cheap and can be prepared in the optically pure form come into consideration, for example, pulegol, 2-phenylcyclohexanol, 2-hydroxy-1,2,2-triphenylethanol, 8-phenylmenthol or compounds containing reactive NH- groups which are cheap and can be prepared in the optically pure form, such as amines, amino acids, lactams or oxazolidinones. Oxazolidinones are preferred, especially preferred are the compounds having formulas B-VIa to B-VId. By selecting the particular antipodes, the absolute stereochemistry on the α-carbonyl carbon of the compound having general formula B-VII is established. In this way, com-

pounds having general formula B-VII to B-XVII or their particular enantiomers ent-B-VII to ent-B-XVII can be obtained in the pure enantiomeric form. If an achiral alcohol, such as ethanol is used as chG^2-H (B-VI), one obtains the racemic compounds rac-B-VII to rac-B-XVII.

Step d (B-VII ⇒ B-VIII):
If the chG^2 group represents one of the chiral auxiliary groups mentioned in step c, then this is recovered by transesterification of B-VII into an alkyl ester having general formula B-VIII. The transesterification is carried out according to methods known to the person skilled in the art. Transesterification with simple alcohols, for example, methanol or ethanol in the presence of corresponding titanium(IV) alcoholates is preferred.

Step e (B-VIII ⇒ B-IX):
The ester in B-VIII is reduced to the alcohol B-IX. Reducing agents known to the person skilled in the art are suitable as reducing agents, for example, aluminum hydrides, for example, lithium aluminum hydride or diisobutylaluminum hydride. The reaction is carried out in an inert solvent, such as diethyl ether, tetrahydrofuran, toluene.

Step e (B-VII ⇒ B-IX):
Alternatively to steps d) and e) the carbonyl group in B-VII can be reduced directly under the conditions given in step e) to the alcohols having general formula B-IX. Here, too, the chiral auxiliary component chG^2-H can be recovered.

Step f (B-IX ⇒ B-X):
For the case where R^3 is not a hydrogen atom, first the primary hydroxyl group in B-IX is oxidized to the corresponding aldehyde using methods known to the person skilled in the art, for example, oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide-pyridine complex, oxidation according to Swern or related methods, for example, using oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides, for example, N-methyl-morpholino-N-oxide in the presence of suitable catalysts, for example, tetrapropylammonium perruthenate in inert solvents can be mentioned. Oxidation according to Swern, as well as with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate are preferred.

Then, the aldehydes thus obtained can be [reduced] to the corresponding alcohols with organometallic compounds having general formula M-R^3, where M stands for an alkali metal, preferably lithium or a divalent metal MX, where X is a halogen and the group R^3 has the meanings given above. Magnesium and zinc are preferred as the divalent metal and halogen X is preferably chlorine, bromine and iodine. [The German sentence has no verb. I put "reduced" in. - Translator]

The free hydroxyl group of the secondary alcohol thus obtained (R^3-H) or for the case R^3 = H the free hydroxyl group in B-IX is protected according to methods known to the person skilled in the art. As protective group PG^{13}, the protective groups known to the person skilled in the art come into consideration, as already given for PG^8 above in step a (A-II ⇒ A-III).

Those protective groups are preferred which can be cleaved off under acidic reaction conditions, for example, methoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl groups.

The tetrahydropyranyl group is especially preferred.

Step g (B-X ⇒ B-XI):
The protective group PG^{12} introduced in step a) is now cleaved off using methods known to the person skilled in the art. If this is a silyl ether, then the reaction with fluorides, for example, tetrabutylammonium fluoride, the hydrogen fluoride-pyridine complex, potassium fluoride or the use of dilute mineral acids, the use of catalytic amounts of acid, for example, para-toluenesulfonic acid, para-toluenesulfonic acid-pyridinium salt, camphorsulfonic acid in alcoholic solutions, preferably in ethanol or isopropanol are suitable for the cleavage.

Step h (B-XI ⇒ B-XII):
For the case where R^{25} is not a hydrogen atom, first the primary hydroxyl group in B-XI is oxidized to the corresponding aldehyde using methods known to the person skilled in the art. For example, oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide/pyridine complex, oxidation according to Swern or related methods, for example, with the use of oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinans,

the use of nitrogen oxides, for example, N-methyl-morpholino-N-oxide in the presence of suitable catalysts, such as tetrapropylammonium perruthenate in inert solvents, can be mentioned. Oxidation according to Swern as well as with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate are preferred.

Then the aldehydes thus obtained can be [reduced] to the corresponding alcohols with organometallic compounds having general formula M-R^{25}, where M stands for an alkali metal, preferably lithium, or a divalent metal MX,. where X represents halogen and the group R^{25} has the meanings given above. Magnesium and zinc are preferred as divalent metal and the halogen X is preferably chlorine, bromine and iodine.

Optionally, the free primary hydroxyl group is converted to a halide according to methods known to the person skilled in the art. Preferred halides are chlorine, but especially bromine and iodine. The substitution of the hydroxyl group by a bromine can be done, for example, with triphenylphosphine/tetrabromomethane, but also according to any other method known to the person skilled in the art. The introduction of an iodine atom can be done from the bromide by substitution, for example, according to Finkelstein with sodium iodide in acetone. Direct conversion of the hydroxyl group into the iodide is also possible, for example, using elemental iodine, imidazole and triphenylphosphine in dichloromethane.

Step i (B-XII ⇒ B-XIII):
If the linking of the C_{13}-C_{16} unit with position 12 of the epothilone group or epothilone fragments is to be done, for example, of a C_7-C_{12} unit by the Wittig reaction, for example, as described in Nature, Volume 387, 268-272 (1997), then, using methods known to the person skilled in the art, starting from halides B-XII, triphenylphosphonium halides (R^{17} = $P(Ph)_3^+Hal^-$), alkyl or arylphosphonate (R^{17} = $P(O)(OQ)_2$) or phosphine oxide (R^{17} = $P(O)Ph_2$) of type B-XII are prepared. Ph here means phenyl; Hal stands for F, Cl, Br or I and Q is a C_1-C_{10} alkyl group or a phenyl group.

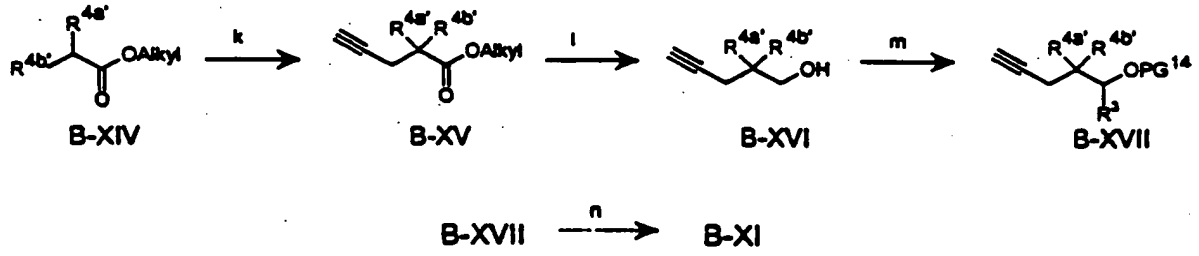
For the preparation of the phosphonium salts, for example, the reaction of the corresponding halides with triphenylphosphine in solvents, such as toluene or benzene, optionally in the presence of a base, such as triethylamine or diisopropylethylamine is suitable.

The preparation of the phosphonate can be carried out, for example, by reaction of the halide B-XI with a metallized dialkylphosphite. The metallization is done usually with strong bases, such as butyllithium.

The preparation of the phosphine oxide can be done, for example, by reacting the halides B-XI with metallized diphenylphosphine and subsequent oxidation. Again, strong bases such as butyllithium are suitable for the metallization. The subsequent oxidation to the phosphine oxide can be done, for example, with dilute aqueous hydrogen peroxide solution.

Alternatively, the compounds having general formula B-XIII can be prepared through the path shown in Scheme 5.

Scheme 5



Step k (B-XIV ⇒ B-XV):
Starting from the inexpensively obtainable ethyl acetate derivatives having general formula B-XIV, in which $R^{4a'}$ and $R^{4b'}$ have the meanings given above, the ester enolate is prepared by the action of strong bases, for example, lithium diisopropylamide, lithium hexamethyldisilazane at low temperatures and reacted with 3-halogen-1-propine, preferably 3-bromo-1-propine to compounds having general formula B-XV.

Step l (B-XV ⇒ B-XVI):
The reduction of the esters B-XV to the alcohol B-XVI is done according to the methods described in step e), preferably using diisobutylaluminum hydride.

Step m (B-XVI ⇒ B-XVII):
In case R^3 is not a hydrogen atom, first the primary hydroxyl group in B-XVI is oxidized to the corresponding aldehyde according to methods known to the person skilled in the art. For example, oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide/pyridine complex, the oxidation according to Swern or related methods, for example, with the use of oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides, for example, N-methyl-morpholino-N-oxide in the presence of suitable catalysts, such as, for example, tetrapropylammonium perruthenate in inert solvents, can be mentioned. Oxidation according to Swern, as well as with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Finally, the aldehydes thus obtained can be [reduced] to the corresponding alcohols with organometallic compounds having general formula M-R^3, where M stands for an alkali metal, preferably lithium, or a divalent metal MX, where X represents a halogen and the group R^3 has the meanings given above. As a divalent metal, magnesium and zinc are preferred and as halogen, X, chlorine, bromine and iodine are preferred.

The free hydroxyl group of the secondary alcohol thus obtained (R^3 = H) or for the case of R^3 = H, the free hydroxyl group in B-XVII is protected according to method known to the person skilled in the art. As protective group PG^{14}, those protective groups known to the person skilled in the art already mentioned above for PG^8 in step a (A-II ⇒ A-III) come into consideration.

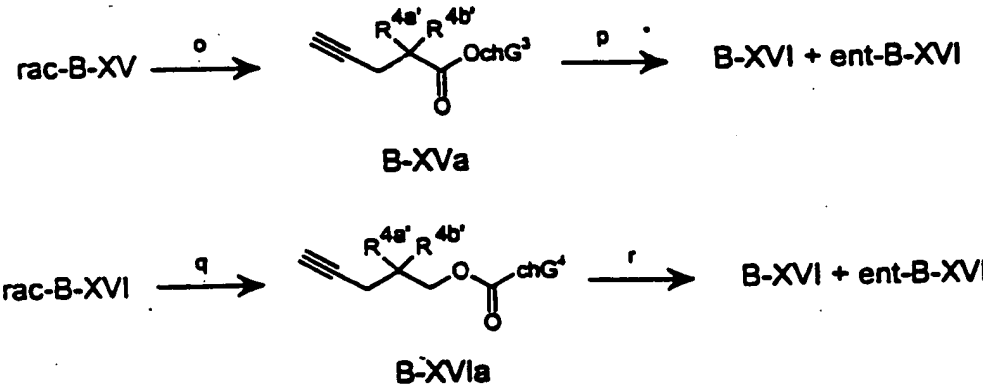
Silicon-containing protective groups, which can be cleaved under acidic reaction conditions or with the use of fluoride, for example, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl groups are preferred.

The tert-butyldimethylsilyl group is especially preferred.

Step n (B-XVII ⇒ B-XI):
The acetylene B-XVII can be deprotonated according to methods known to the person skilled in the art and the obtained acetylide can be reacted with formaldehyde to form an alcohol of general formula B-XI. Alkyl alkali compounds, for example, butyllithium or other strong bases, for example, alkali hexamethyldisilazane or lithium diisopropylamide are suitable for deprotonation. n-Butyllithium is preferred.

Using the method described in Scheme 5, first the racemic compounds, rac-B-XI, are obtained. Optionally, the steps which rac-B-XV and rac-B-XVI go through according to Scheme 6 offer the possibility of chemical resolution of the racemate and thus also access to the enantiomeric compounds B-XVI or ent-B-XVI as long as $R^{4a'}$ is not identical with $R^{4b'}$.

Scheme 6



Step o (rac-B-XV ⇒ B-XVa):
The racemic compound rac-B-XV can be transesterified with a chiral alcohol chG^3-OH, which can be obtained in the optically pure form, using methods known to the person skilled in the art, for example, the methods named under step d) to a mixture of the diastereomeric esters B-XVa and can be separated with simple chromatographic methods. For example, pulegol, 2-phenylcyclohexanol, 2-hydroxy-1,2,2-triphenylethanol, 8-phenylmenthol come into consideration as chiral alcohols.

Step p (B-XVa ⇒ B-XVI and ent-B-XVI):
The pure diastereomeric esters B-XVa can be reduced to the alcohols B-XVI and ent-B-XVI using the method described under step e), where the auxiliary component chG^3-OH described in step o) can be recovered.

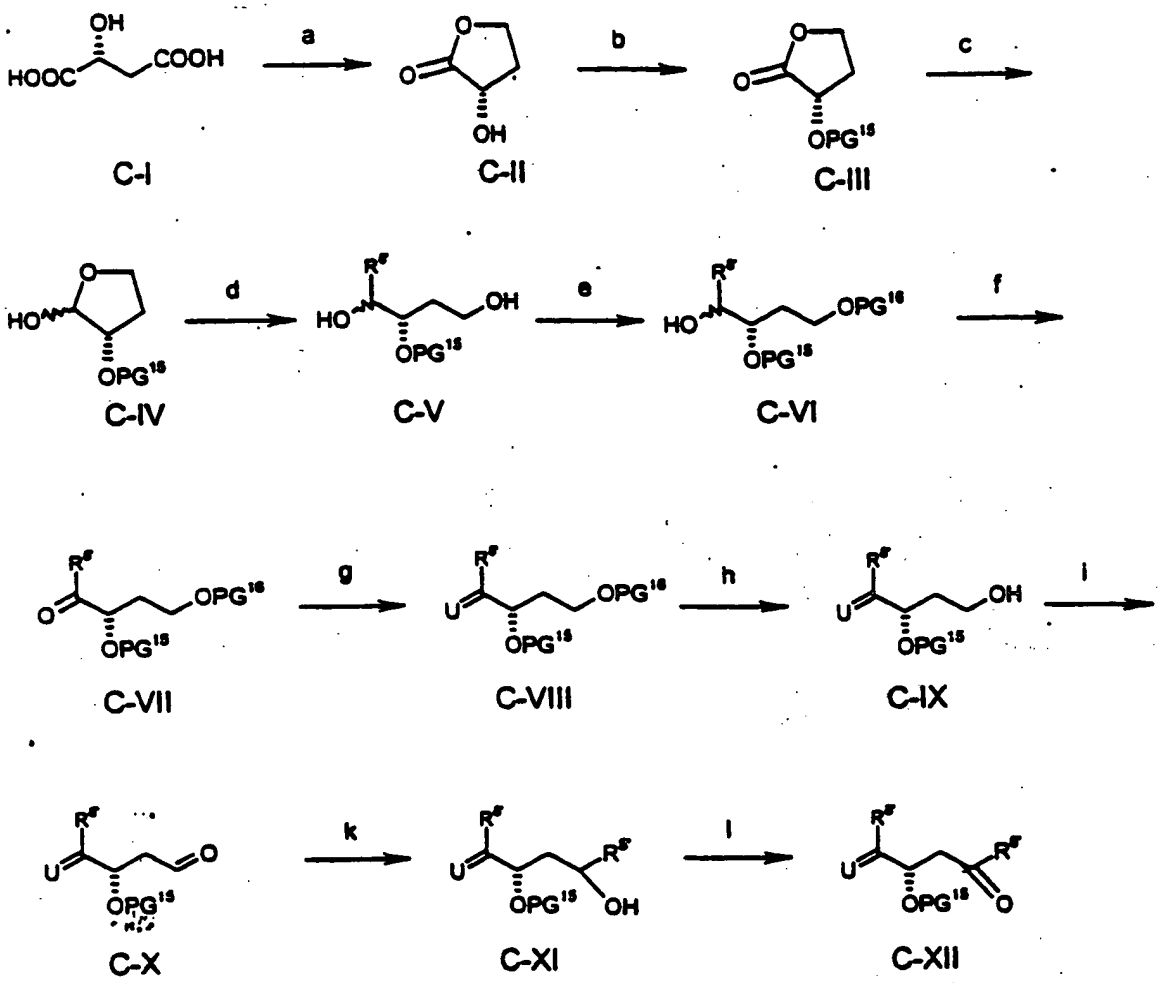
Step q (rac-B-XVI ⇒ B-XVIa):
The racemic compound rac-B-XVI can be converted with a chiral acid chG^4-CO_2H, which can be obtained in the optically pure form, with its ester, anhydride or acid halide to a mixture of diastereomeric esters B-XVIa, using the methods known to the person skilled in the art, and can be separated with simple chromatographic methods. As chiral acids, especially malic acid, tartaric acid or their derivatives come into consideration.

Step r (B-XVIa ⇒ B-XVI and ent-B-XVI):
The diastereomerically pure esters B-XVIa can be reduced to the alcohols B-XVI and ent-B-XVI according to the method described in step e), or can be saponified according to methods known to the person skilled in the art, where, in the latter case, the auxiliary component chG^4-CO_2H described in step u can be recovered.

Preparation of partial fragments C (see also WO 99/07692):
Partial fragments C can be prepared from inexpensive, cheaply obtainable malic acid in an efficient manner with high optical purity (> 99.5% ee).

The synthesis is described in the following Scheme 7 on the example of L-(-)malic acid (C-I). Starting from D(+)-malic acid (ent-C-I), the corresponding enantiomeric compounds (ent-C-II to ent-C-XI) are obtained and starting from racemic malic acid (rac-C-I), the corresponding racemic compounds are obtained (rac-C-II to rac-C-XI).

Scheme 7



Step a (malic acid C-I ⇒ C-II):

L-(-)-malic acid is converted to the hydroxylactone C-II according to a method known from the literature (Liebigs Ann. Chem. 1993, 1273-1278).

Step b (C-II ⇒ C-III):

The free hydroxyl group in compound C-II is protected according to methods known to the person skilled in the art. As protective group PG^{15}, those protective groups known to the person skilled in the art come into consideration as they were already named above for PG^{8} in step a (A-II ⇒ A-III).

Those protective groups are preferred which can be cleaved under the action of fluoride, but are stable under weakly acidic reaction conditions, such as, for example, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, or triisopropylsilyl groups.

Especially preferred are the tert-butyldiphenylsilyl and the tert-butyldimethylsilyl groups.

Step c (C-III ⇒ C-IV):
The lactone C-III is reduced to the lactol C-IV according to methods known to the person skilled in the art. As reducing agent, aluminum hydrides modified in their reactivity are suitable, for example, diisobutylaluminum hydride. The reaction is carried out in an inert solvent, for example, toluene, preferably at low temperatures (-20 to -100°C).

Step d (C-IV ⇒ C-V):
The reaction of the lactol C-IV to compounds having formula C-V is done with organometallic compounds having general formula M-$R^{8'}$, where M stands for an alkali metal, preferably lithium, or a divalent metal MX, where X is a halogen and $R^{8'}$ has the meanings given above. Magnesium and zinc are preferred as the divalent metal and chlorine, bromine and iodine are preferred as halogen X.

Step e (C-V ⇒ C-VI):
The primary hydroxyl group in compound C-V is protected selectively in comparison to the secondary hydroxyl group using methods known to the person skilled in the art. As protective group PG^{16}, those protective groups known to the person skilled in the art come into consideration as they were already named before for PG^{8} in step a (A-II ⇒ A-III).

Those protective groups are preferred which can be cleaved under weakly acidic reaction conditions, for example, the trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl groups.
[Translator's note: the latter compound was listed above as being stable under weakly acidic reaction conditions. - Translator]
The tert-butyldimethylsilyl group is especially preferred.

Step f (C-VI ⇒ C-VII):
The oxidation of the secondary alcohol in C-VI to the ketone C-VII is done according to methods known to the person skilled in the art. For example, oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide/pyridine complex, oxidation according to Swern or related methods, for example, using oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides, such as N-methylmorpholino-N-oxide in the presence of suitable catalysts, for example, tetrapropylammonium perruthenate in inert solvents should be mentioned as examples. Oxidation according to Swern is preferred.

Step g (C-VII ⇒ C-VIII):
For compounds in which U is equal to $CR^{11'}R^{12'}$, this group is prepared according to methods known to the person skilled in the art. For this purpose, methods, for example, the Wittig or Wittig/Horner reaction, the addition of an organometallic compound $MCHR^{11'}R^{12'}$ with the elimination of water are suitable. The Wittig and Wittig/Horner reactions are preferred with the use of phosphonium halides of the type $CR^{11'}R^{12'}P(Ph)_3{}^+Hal^-$ or phosphonates of the type $CR^{11'}R^{12'}P(O)(Oalkyl)_2$ with Ph being phenyl, $R^{11'}$, $R^{12'}$ and halogen, having the meanings given above, with strong bases, for example, n-butyllithium, potassium tert-butanolate, sodium methanolate, sodium hexamethyldisilazane are preferred; the preferred base is n-butyllithium.

For compounds in which U represents two alkoxy groups OR^9 or a C_2-C_{10} alkylene-α,ω-dioxy group, the ketone is ketalized according to methods known to the person skilled in the art, for example, using an alcohol HOR^9 or a C_2-C_{10} alkylene-α,ω-diol with acid catalysis.

Step h (C-VIII ⇒ C-IX):
The protective group PG^{16} introduced under e is now cleaved selectively in the presence of PG^{15} according to methods known to the person skilled in the art. If it is a protective group that can be cleaved off with acid, the cleavage is preferably carried out under weakly acidic conditions, for example, by reaction with dilute organic acids in inert solvents. Acetic acid is preferred.

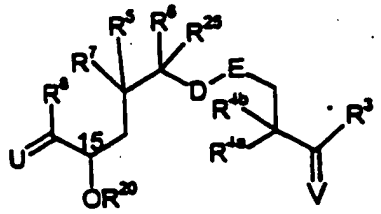
Step i (C-IX ⇒ C-X):
The oxidation of the primary alcohol in C-IX to the aldehyde having general formula C-X is done according to methods known to the person skilled in the art. For example, let us mention oxidation with pyridinium chlorochromate, pyridinium dichromate, chromium trioxide/pyridine complex, the oxidation according to Swern or related methods, for example, using oxalyl chloride in dimethylsulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides, for example, N-methyl-morpholino-N-oxide in the presence of suitable catalysts, for example, tetrapropylammonium perruthenate in inert solvents. Oxidation according to Swern, as well as with N-methyl-morpholino-N-oxide using tetrapropylammonium perruthenate is preferred.

Step k (C-X ⇒ C-XI):
The reaction of the aldehydes C-X to alcohols having general formula C-XI is done according to methods known to the person skilled in the art, with organometallic compounds having general formula M-$R^{5'}$, where M stands for an alkali metal, preferably lithium or a divalent metal MX, where X represents a halogen and the group $R^{5'}$ has the meaning given above. Magnesium and zinc are preferred as a divalent metal, and chlorine, bromine and iodine are preferred as the halogen X.

Step l (C-XI ⇒ C-XII):
The oxidation of the alcohol C-XI to the ketone having general formula C-XII is done according to the method given under k) or by Jones oxidation. The oxidation according to Jones is preferred.

Preparation of the partial fragments ABC and their cyclization to I:

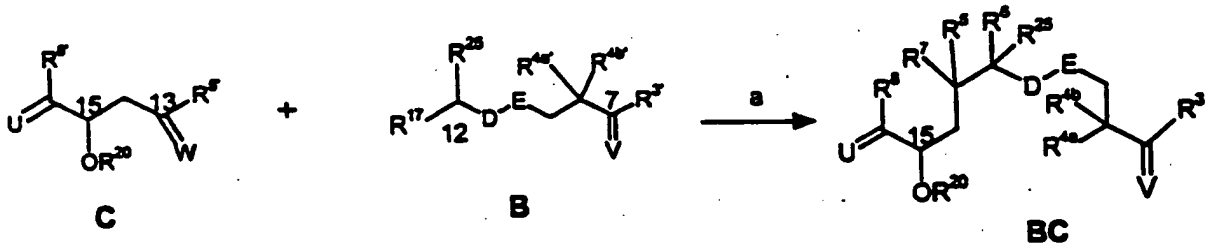
Partial fragments having general formula AB



BC,

where R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^{20}, D, E, U and V have the meanings already given above, are obtained from the fragments B and C described before according to the method indicated in Scheme 8.

Scheme 8

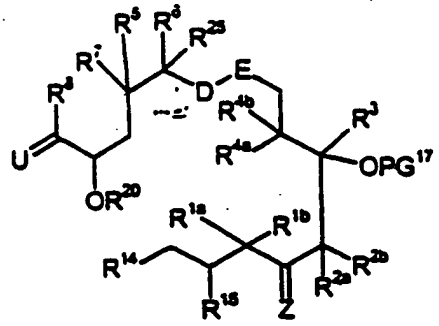


C **B** **BC**

Step a (B + C ⇒ BC):

The compound B, in which R^{17} has the meaning of a Wittig salt and any additional carbonyl groups present are protected, is deprotonated by a suitable base, for example, n-butyllithium, lithium diisopropylamide, potassium tert-butanolate, sodium or lithium hexamethyldisilazide and reacted with a compound C, where W stands for an oxygen atom.

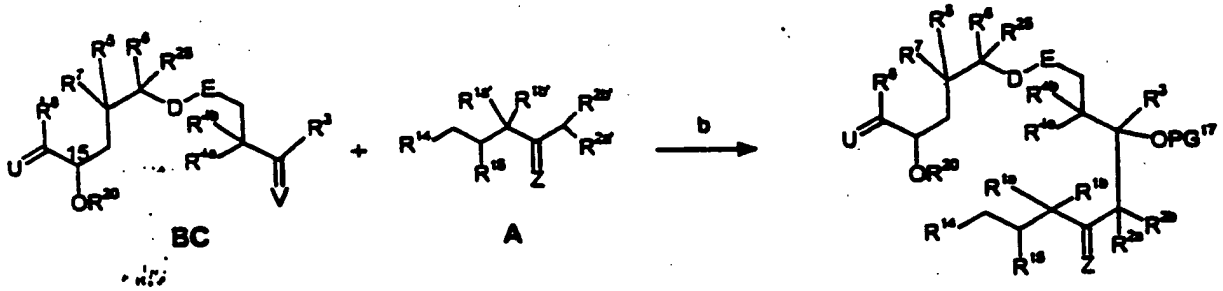
Partial fragments having the general formula ABC



ABC,

where R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^8, R^{14}, R^{15}, D, E, U and Z are prepared from the fragments AB and C described above, according to the method shown in Scheme 9.

Scheme 9



BC **A** **ABC**

Step b (BC + A ⇒ ABC):

The compound BC, where V stands for an oxygen atom and any additional carbonyl groups present are protected, is alkylated with the enolate of a carbonyl compound having general formula A, where Z stands for an oxygen atom. The enolate is prepared by the action of strong bases, such as lithium diisopropylamide, lithium hexamethyldisilazane at low temperatures.

Step c (ABC ⇒ I):
The compounds ABC, in which R^{14} is a carboxylic acid CO_2H and R^{20} represents a hydrogen atom, are reacted according to methods known to the person skilled in the art for the formation of large macrolides, to form compounds having formula I, in which Y has the meaning of an oxygen atom. Preferably, the method described in "Reagents for Organic Synthesis, Volume 16, p. 353" is used with 2,4,6-trichlorobenzoic acid chloride and suitable bases, for example, triethylamine, 4-dimethylaminopyridine, sodium hydride.

Step d (ABC ⇒ I):
The compounds ABC, in which R^{14} is a CH_2OH group and R^{20} is a hydrogen atom, can be reacted, preferably using triphenylphosphine and azodiesters, for example, azodicarboxylic acid diethyl ester to compounds having formula I, in which Y has the meaning of two hydrogen atoms.

The compounds ABC in which R^{14} is a CH_2OSO_2alkyl or CH_2OSO_2aryl or CH_2OSO_2aralkyl group and R^{20} represents a hydrogen atom, can be cyclized after deprotonation with suitable bases, for example, sodium hydride, n-butyllithium, 4-dimethylaminopyridine, Hünig base, alkali hexamethyldisilazanes, to form compounds having formula I, in which Y has the meaning of two hydrogen atoms.

The invention is also concerned with this method for the preparation of compounds having general formula I, as well as with the new intermediate products having general formulas B, C, BC and ABC, including all stereoisomers of these compounds and also their mixtures.

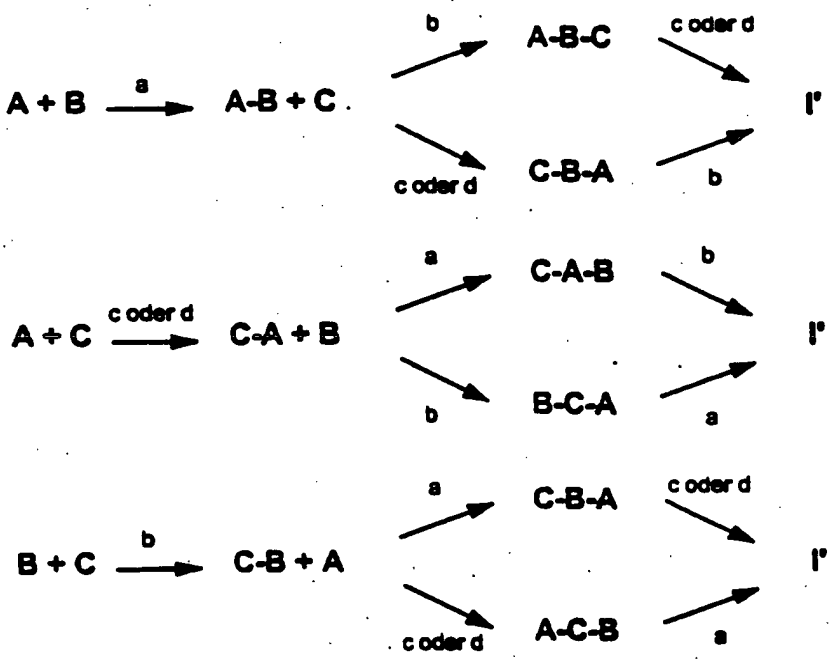
The flexible functionalization of the described units A, B and C also provides a sequence of linking which deviates from that described above, which leads to units ABC. These methods are summarized in the following table.

possibilities of linking	linking methods a to d	prerequisites
A + B = A-B	a: aldol	Z = V = oxygen
B + C = B-C	B: Wittig (Scheme 8)	W = oxygen and R^{17} = Wittig salt or phosphine oxide or phosphonate
A + C = A-C	c: esterification (for example, 2,4,6-trichlorobenzoyl chloride/4-dimethylaminopyridine) d: etherification (for example, Mitsunobu)	R^{14} = CO_2R^{15} or COHal and R^{20} = hydrogen R^{14} = CH_2OH and R^{20} = hydrogen or SO_2-alkyl or SO_2-aryl or SO_2-aralkyl

According to these methods, units A, B and C can be linked as shown in Scheme 10:

Scheme 10

oder = or



The free hydroxyl groups in I, A, B, C, AB, ABC can be changed further functionally by etherification or esterification, and the free carbonyl groups by ketalization, enol ether formation or reduction.

The invention is also concerned with these methods for the preparation of epothilone derivatives having the general formula.

Biological effects and areas of application of the new derivatives:

The new compounds having formula I are valuable drugs. They interact with tubulin, in which they stabilize the formed microtubuli and thus are able to influence cell division phase-specifically. This applies especially to fast-growing, neoplastic cells, the growth of which is largely uninfluenced by intercellular control mechanisms. Active ingredients of this type are in principle suitable for the treatment of malignant tumors. As an area of application, let us mention, for example, the therapy of ovarian, gastric, colon, adeno, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytary and myelocytary leukemia. The compounds according to the invention, due to their properties, are suitable mainly for anti-angiogenesis therapy, as well as for the treatment of chronic inflammatory diseases, for example, psoriasis or arthritis. In order to avoid uncontrolled cell growth on medical implantates, as well as better compatibility of these, in principle, they can be applied onto or incorporated into the polymeric materials used for this. The compounds according to the invention can be used alone or, in order to achieve additive or synergistic effects, in combination with other principles and substances classes that can be used in tumor therapy.

Let us give, as examples, the combinations with

- ⇒ platinum complexes, for example, cisplatin, carboplatin,
- ⇒ intercalating substances, for example, from the class of anthracyclines, for example, doxorubicin or from the class of antrapyrazoles, for example, Cl-941,
- ⇒ substances that interact with tubulin, for example, from the class of vinca-alkaloids, for example, vincristine, vinblastine or from the class of taxanes, for example, taxol, taxotere or from the class of macrolides, for example, rhizoxin or other compounds, such as colchicin, combretastatin A-4,
- ⇒ DNA topoisomerase inhibitors, for example, camptothecin, etoposide, topotecan, teniposide,
- ⇒ folate or pyrimidine antimetabolites, for example, lometrexol, gemcitubin [gemci-tabine?],
- ⇒ DNA-alkylating compounds, for example, adozelesin, dystamycin A,
- ⇒ inhibitors of growth factors (for example, of PDGF, EGF, TGFb, EGF) such as, for example, somatostatin, suramin, bombesin antagonists,
- ⇒ inhibitors of protein, tyrosine kinase or protein kinases A or C, for example, erbsta-tin, genistein, staurosporin, llmofosin [sic], 8-Cl-cAMP,

- ⇒ antihormones from the class of antigestagens, for example, mifepristone, onapristone or the class of antiestrogens, for example, tamoxifen or from the class of antiandrogens, for example, cyproterone acetate,
- ⇒ metastasis-inhibiting compounds, for example, from the class of eicosanoids, such as PGI_2, PGE_1, 6-oxo-PGE_1 as well as their stable derivatives, for example, iloprost, cicaprost, misoprostol),
- ⇒ oncogenic RAS protein inhibitors, which influence mitotic signal transduction, such as, for example, inhibitors of farnesyl protein transferase,
- ⇒ natural or artificially produced antibodies, which are directed against factors or their receptors that promote tumor growth, for example, erbB2 antibodies.

The invention is also concerned with drugs based on pharmaceutically compatible compounds having general formula I, that is, those which are not toxic at the doses used, optionally together with the usual additives and carriers.

The compounds according to the invention can be processed to pharmaceutical preparations according to methods in galenics for enteral, percutaneous, parenteral or local application. They can be administered in the form of tablets, coated tablets, gel capsules, granules, suppositories, implantates, injectable sterile aqueous or oily solutions, suspensions or emulsions, salves, creams and gels.

The active ingredient or ingredients can be mixed with additives usually used in galenics, such as gum arabic, talc, starch, mannitol, methylcellulose, lactose, surfactants, such as Tweens or Myrj, magnesium stearate, aqueous or nonaqueous carriers, paraffin derivatives, wetting agents, dispersing agents, emulsifiers, preservatives and aromas for taste correction (for example, essential oils).

Thus, the invention is also concerned with the pharmaceutical compositions which contain at least one compound according to the invention as active ingredient. A dosage unit contains approximately 0.1-100 mg of active ingredient(s). The dosage of the compounds according to the invention for humans lies at about 0.1-1000 mg per day.

The following examples serve for closer explanation of the invention without these representing a limitation:

Example 1
(4S,7R,8S,9S,13(E),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

Example 1a
(3S)-1-Oxa-2-oxo-3-(tetrahydropyran-2-(RS)-yloxy)-4,4-dimethyl-cyclopentane
A solution of 74.1 g (569 mmole) of D-(-)pantolactone in 1 L anhydrous dichloromethane is treated in a dry argon atmosphere with 102 mL of 3,4-dihydro-2H-pyran, 2 g of p-toluenesulfonic acid pyridinium salt and stirred for 16 hours at 23°C. It is poured into a saturated sodium hydrogen carbonate solution, the organic phase is separated and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on approximately 5 kg of fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 119.6 g (558 mmole, 98%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.13 (3H), 1.22 (3H), 1.46-1.91 (6H), 3.50-3.61 (1H), 3.86 (1H), 3.92 (1H), 4.01 (1H), 4.16 (1H), 5.16 (1H) ppm.

Example 1b
(2RS,3S)-1-Oxa-2-hydroxy-3-(tetrahydropyran-2(RS)-yloxy)-4,4-dimethyl-cyclopentane
A solution of 117.5 g (548 mmole) of the compound prepared according to Example 1a in 2.4 L of anhydrous toluene is cooled in a dry argon atmosphere to -70°C and 540 mL of a 1.2 molar solution of diisobutylaluminum hydride in toluene is added to it over a period of 1 hour. Stirring is continued for another 3 hours at -70°C. The mixture is allowed to warm up to -20°C, saturated ammonium chloride solution and water are added and the precipitated aluminum salts are separated by filtration through Celite. The filtrate is washed with water and saturated sodium chloride solution and dried over magnesium sulfate. After filtration and removal of the solvent, 111.4 g (515 mmole, 94%) of the compound in the title are isolated as a colorless oil, which is reacted further without purification.

IR ($CHCl_3$): 3480, 3013, 2950, 2874, 1262, 1133, 1074, 1026 and 808 cm^{-1}.

Example 1c

(3S)-2,2-Dimethyl-3-(tetrahydropyran-2(R)-yloxy)-pent-4-en-1-ol and (3S)-2,2-dimethyl-3-(tetrahydropyran-2(S)-yloxy)-pent-4-en-1-ol

A suspension of 295 g of methyl triphenylphosphonium bromide in 2.5 L anhydrous tetrahydrofuran is treated under a dry argon atmosphere at -60°C with 313 mL of a 2.4 molar solution of n-butyllithium in n-hexane, the mixture is allowed to warm up to 23°C, stirred for one hour and then cooled to 0°C. Then, a solution of 66.2 g (306 mmole) of the compound prepared according to Example 1b in 250 mL of tetrahydrofuran, the mixture is allowed to warm to 23°C and is stirred for 18 hours. It is poured into a saturated sodium hydrogen carbonate solution, extracted several times with dichloromethane and the combined organic extracts are dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on approximately 5 L fine silica gel with a gradient system consisting of n-hexane and ethyl acetate. Thus, 36.5 g (170 mmole, 56%) of the nonpolar and 14.4 g (67.3 mmole, 22%) of the polar THP isomer of the compound in the title as well as 7.2 g (33.3 mmole, 11%) of the starting material are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$), nonpolar isomer: δ = 0.78 (3H), 0.92 (3H), 1.41-1.58 (4H), 1.63-1.87 (2H), 3.18 (1H), 3.41 (1H), 3.48 (1H), 3.68 (1H), 3.94 (1H), 4.00 (1H), 4.43 (1H), 5.19 (1H), 5.27 (1H), 5.75 (1H) ppm.
^{1}H-NMR ($CDCl_3$, polar isomer: δ = 0.83 (3H), 0.93 (3H), 1.42-1.87 (6H), 2.76 (1H), 3.30 (1H), 3.45 (1H), 3.58 (1H), 3.83 (1H), 3.89 (1H), 4.65 (1H), 5.12-5.27 (2H), 5.92 (1H) ppm.

Example 1d

(3S)-1-(tert-Butyldiphenylsilyloxy)-2,2-dimethylpentane-3-(tetrahydropyran-2-yloxy)-pent-4-ene

A solution of 59.3 g (277 mmole) of the THP isomer mixture prepared according to Example 1c in 1000 mL of anhydrous dimethylformamide is treated under a dry argon atmosphere with 28 g of imidazole, 85 mL of tert-butyldiphenylchlorosilane and the mixture is stirred for 16 hours at 23°C. Then it is poured into water, extracted several times with dichloromethane, the combined organic extracts are washed with water and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on fine silica gel

with a gradient system of n-hexane and ethyl acetate. Thus, 106.7 g (236 mmole, 85%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.89 (3H), 0.99 (3H), 1.08 (9H), 1.34-1.82 (6H), 3.40 (1H), 3.51 (2H), 3.76 (1H), 4.02 (1H), 4.67 (1H), 5.18 (1H), 5.23 (1H), 5.68 (1H), 7.30-7.48 (6H), 7.60-7.73 (4H) ppm.

Example 1e

(3S)-1-(tert-Butyldiphenylsilyloxy)-2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-pentan-5-ol

A solution of 3.09 g (6.83 mmole) of the compound prepared according to Example 1d in 82 mL of tetrahydrofuran is treated under an atmosphere of dry argon at 23°C with 13.1 mL of a 1 molar solution of borane in tetrahydrofuran, and the reaction is allowed to proceed for 1 hour. Then 16.4 mL of a 5% sodium hydroxide solution as well as 8.2 mL of a 30% hydrogen peroxide solution are added under cooling in ice and stirring is continued for another 30 minutes. The mixture is poured into water, extracted several times with ethyl acetate, the combined organic extracts are washed with water, saturated sodium chloride solution and dried over magnesium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 1.78 g (3.78 mmole, 55%) of the compound in the title are isolated as a chromatographically separable mixture of the two THP epimers, as well as 0.44 g (1.14 mmole, 17%) of the compound in the title from Example 6, all as colorless oil.

^{1}H-NMR ($CDCl_3$), nonpolar THP isomer: δ = 0.80 (3H), 0.88 (3H), 1.10 (9H), 1.18-1.80 (9H), 3.27 (1H), 3.39 (1H), 3.48 (1H), 3.64 (1H), 3.83 (1H), 3.90-4.08 (2H), 4.49 (1H), 7.31-7.50 (6H), 7.58-7.73 (4H) ppm.
^{1}H-NMR ($CDCl_3$), polar THP isomer: δ = 0.89 (3H), 0.98 (3H), 1.08 (9H), 1.36-1.60 (4H), 1.62-1.79 (3H), 1.88 (1H), 2.03 (1H), 3.37 (1H), 3.50 (1H), 3.57 (1H), 3.62-3.83 (4H), 4.70 (1H), 7.30-7.48 (6H), 7.61-7.73 (4H) ppm.

Example 1f

(3S)-1-(tert-Butyldiphenylsilyloxy)-2,2-dimethyl-3-hydroxy-pent-4-ene

A solution of 106.7 g (236 mmole) of the compound prepared according to Example 1d in 1.5 L anhydrous ethanol is treated under a dry argon atmosphere with 5.9 g of pyridinium-p-

toluenesulfonate, followed by heating for 6 hours at 50°C. After the removal of the solvent, the residue is chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 82.6 g (224 mmole, 95%) of the compound in the title are isolated as a colorless oil, which additionally contains approximately 5 g of ethoxytetrahydropyran.

^{1}H-NMR ($CDCl_3$ of an analytical sample: δ = 0.89 (6H), 1.08 (9H), 3.45 (1H), 3.49 (1H), 3.58 (1H), 4.09 (1H), 5.21 (1H), 5.33 (1H), 5.93 (1H), 7.34-7.51 (6H), 7.63-7.73 (4H) ppm.

Example 1g

(3S)-1-(tert-Butyldiphenylsilyloxy)-2,2-dimethyl-pentane-3,5-diol

A solution of 570 mg (1.55 mmole) of the compound prepared according to Example 1f is treated analogously to Example 1e and, after work-up and purification, 410 mg (1.06 mmole, 68%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.82 (3H), 0.93 (3H), 1.08 (9H), 1.56-1.79 (2H), 3.11 (1H), 3.50 (2H), 3.78-3.92 (3H), 4.02 (1H), 7.34-7.51 (6H), 7.61-7.71 (4H) ppm.

Example 1h

4(S)-[2-Methyl-1-(tert-butyldiphenylsilyloxy)-prop-2-yl]-2,2-dimethyl-[1,3]dioxane

A solution of 100 mg (0.212 mmole) of the compounds prepared according to Example 1e in 2.6 mL of anhydrous acetone, is treated under a dry argon atmosphere with 78.9 mg of copper(II) sulfate, and a spatula-tip of p-toluenesulfonic acid monohydrate, followed by stirring for 16 hours at 23°C. Saturated sodium hydrogen carbonate solution is added, the mixture is extracted with diethyl ether several times, washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 24 mg (56 μmole, 27%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.83 (3H), 0.89 (3H), 1.07 (9H), 1.30 (1H), 1.36 (3H), 1.44 (3H), 1.71 (1H), 3.24 (1H), 3.62 (1H), 3.86 (1H), 3.91-4.03 (2H), 7.31-7.48 (6H), 7.61-7.74 (4H) ppm.

Variant II

320 mg (0.88 mmole) of the compound prepared according to Example 1g is treated analogously to Example 1h; Variant I, and after work-up and purification, 234 mg (0.548 mmole, 62%) of the compound in the title, are isolated.

Variant III

A solution of 5.60 g (14.5 mmole) of the compound prepared according to Example 1g in 250 mL of anhydrous dichloromethane is treated in a dry argon atmosphere with 10 mL of 2,2-dimethoxypropane, 145 mg of camphor-10-sulfonic acid, followed by stirring for 6 hours at 23°C. Then, triethylamine is added, the mixture is diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After filtration and removal of the solvent, the residue is chromatographed on fine silica gel with a mixture of n-hexane and ethyl acetate. Thus, 5.52 g (12.9 mmole, 89%) of the compound in the title are isolated as a colorless oil.

Example 1i

(4S)-4-(2-Methyl-1-hydroxy-prop-2-yl)-2,2-dimethyl-[1,3]dioxane

A solution of 5.6 g (13.1 mmole) of the compound prepared according to Example 1h, in 75 mL of anhydrous tetrahydrofuran, is treated under a dry argon atmosphere with 39 mL of 1 molar solution of tetrabutylammonium fluoride in tetrahydrofuran, followed by heating for 16 hours at 50°C. Then, saturated sodium hydrogen carbonate solution is added, followed by extraction several times with ethyl acetate, washing with saturated sodium chloride solution and drying over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 2.43 g (12.9 mmole, 99%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.87 (3H), 0.90 (3H), 1.35 (1H), 1.37 (3H), 1.43 (3H), 1.77 (1H), 2.93 (1H), 3.36 (1H), 3.53 (1H), 3.79 (1H), 3.87 (1H), 3.96 (1H) ppm.

Example 1k

(4S)-4-(2-Methyl-1-oxo-prop-2-yl)-2,2-dimethyl-[1,3]dioxane

A solution of 0.13 mL oxalyl chloride in 5.7 mL of anhydrous dichloromethane is cooled under a dry argon atmosphere to -70°C, 0.21 mL of dimethylsulfoxide, the solution of 200 mg (1.06 mmole) of the compound prepared according to Example 1i in 5.7 ml of anhydrous dichloromethane is added and the mixture is stirred for 0.5 hours. Then, 0.65 mL of triethylamine are added, the mixture is allowed to react for 1 hour at -30°C and then n-hexane and saturated sodium hydrogen carbonate solution are added. The organic phase is separated, the aqueous phase is extracted several times with n-hexane, the combined organic extracts are washed with water and dried over magnesium sulfate. The residue obtained after filtration and removal of the solvent is reacted further without purification.

Example 1l

(4S)-4-((3RS)-2-Methyl-3-hydroxy-pent-2-yl)-2,2-dimethyl-[1,3]dioxane

A solution of 900 mg (4.83 mmole) of the compound prepared according to Example 1k in 14 mL of anhydrous diethyl ether is treated under a dry argon atmosphere at 0°C with 2.42 mL of a 2.4 molar solution of ethylmagnesium bromide in diethyl ether, allowing the mixture to warm up to 23°C, followed by stirring for 16 hours. Then, saturated ammonium chloride solution is added, the organic phase is separated and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 863 mg (3.99 mmole, 83%) of the chromatographically separable 3R- and 3S-epimers of the compound in the title as well as 77 mg of the title compound described in Example 1i are isolated, each as a colorless oil.

^{1}H-NMR ($CDCl_3$) nonpolar isomer: δ = 0.86 (3H), 0.89 (3H), 1.03 (3H), 1.25-1.37 (2H), 1.37 (3H), 1.46 (3H), 1.49 (1H), 1.84 (1H), 3.35 (1H), 3.55 (1H), 3.81-4.02 (3H) ppm.
^{1}H-NMR ($CDCl_3$) polar isomer: δ = 0.72 (3H), 0.91 (3H), 0.99 (3H), 1.25-1.44 (2H), 1.38 (3H), 1.43-1.60 (1H), 1.49 (3H), 1.76 (1H), 3.39 (1H), 3.63 (1H), 3.79-4.03 (3H) ppm.

Example 1m

(4S)-4-(2-Methyl-3-oxo-pent-2-yl)-2,2-dimethyl-[1,3]dioxane

A solution of 850 mg (3.93 mmole) of a mixture of the compounds prepared according to Example 1l in 63 mL of anhydrous dichloromethane is treated with a molecular sieve (4A, approximately 80 spheres), 690 mg of N-methyl-morpholino-N-oxide, 70 mg of tetrapropyl-ammonium perruthenate, followed by stirring for 16 hours at 23°C under a dry argon atmosphere. The mixture is evaporated and the obtained crude product is purified by chromatography on approximately 200 mL of fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 728 mg (3.39 mmole, 86%) of the compound in the title are isolated as colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.07 (3H), 1.11 (3H), 1.31 (3H), 1.32 (3H), 1.41 (3H), 1.62 (1H), 2.52 (2H), 3.86 (1H), 3.97 (1H), 4.05 (1H) ppm.

Example 1n

4-tert-Butyldimethylsilyloxy-but-2-in-1-ol

A solution of 100 g of 2-butin-1-ol and 158 g of imidazole in 300 mL of dimethylformamide is treated at 0°C under nitrogen by dropwise addition of a solution of 175 g of tert-butyl-dimethylsilyl chloride in 100 mL of a 1:1 mixture of hexane and dimethylformamide, followed by stirring for 2 hours at 0°C and 16 hours at 22°C. The reaction mixture is diluted with 2.5 L of ether, washed once with water, once with 5% sulfuric acid, once with water, once with saturated sodium hydrogen carbonate solution and to neutrality with half-saturated sodium chloride solution. After drying over sodium sulfate and filtration, the mixture is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-40% ether, 74.3 g of the compound in the title are obtained as a colorless oil.

IR (film): 3357, 2929, 2858, 1472, 1362, 1255, 1132, 1083, 1015, 837, 778 cm^{-1}.

Example 1o

(4R,5S,2'S)-4-Methyl-5-phenyl-3-[1-oxo-2-methyl-6-(tert-butyldimethylsilyloxy)-hex-4-in-1-yl]-2-oxazolidinone

To 21 g of a solution of the silyl ether prepared in Example 1n in 125 mL of toluene, 11.3 mL of lutidine are added under nitrogen. Then, the mixture is cooled to -40°C and, at this temperature, 17.7 mL of trifluoromethanesulfonic acid anhydride are added dropwise. The mixture is diluted with 100 mL of hexane and stirred for 10 minutes. This solution is added under nitrogen through a reversed sintered glass filter to a solution which was prepared from 17.8 g of hexamethyldisilazane in 140 mL of tetrahydrofuran with 73.5 mL of a 1.6 M solution of butyllithium in hexane at -60°C (10 minutes of additional stirring time) and 23.3 g of (4R,5S)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone in 62 mL of tetrahydrofuran (30 minutes additional stirring time). Stirring is continued for 1 hour at -60°C and then 6 mL of acetic acid in 5 mL of tetrahydrofuran are added; the reaction mixture is allowed to warm up to 22°C. It is poured into 80 mL of water and extracted 3 times with ether. The combined organic phases are washed twice with saturated sodium chloride solution and dried over sodium sulfate. After filtration, it is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-20% ether, 16.0 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.10 (6H), 0.90 (9H), 0.92 (3H), 1.28 (3H), 2.47 (1H), 2.61 (1H), 3.96 (1H), 4.26 (2H), 4.78 (1H), 5.68 (1H), 7.31 (1H), 7.3-7.5 (3H) ppm.

Example 1p

(2S)-2-Methyl-6-(tert-butyldimethylsilyloxy)-4-hexinoic acid ethyl ester

To a solution of 39.3 g of the alkylation product prepared according to Example 1o in 120 mL of ethanol, 9.0 mL of titanium(IV) ethylate are added under nitrogen followed by heating under reflux for 4 hours. The reaction mixture is evaporated in vacuum and the residue is dissolved in 100 mL of ethyl acetate. Three mL of water are added, followed by stirring for 20 minutes, the precipitate is filtered off under suction and washed thoroughly with ethyl acetate. The filtrate is evaporated, 200 mL of hexane are added to it and the precipitate is filtered off. The precipitate is washed thoroughly with hexane. The filtrate is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-20% ether, 25.4 g of the compound in the title is obtained as a colorless oil.

^{1}H-NMR (CD_2Cl_2): δ = 0.10 (3H), 0.90 (9H), 1.2-1.3 (6H), 2.37 (1H), 2.54 (1H), 2.60 (1H), 4.12 (2H), 4.27 (2H) ppm.

Example 1q

(2S)-2-Methyl-6-(tert-butyldimethylsilyloxy)-hexanoic acid ethyl ester

A solution of 10.5 g of the ester prepared according to Example 1p in 200 mL of ethyl acetate is treated with 1 g of 10% palladium on carbon and the mixture is stirred for 3 hours at 22°C in a hydrogen atmosphere. Then the catalyst is filtered off, washed thoroughly with ethyl acetate and the filtrate is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-10% ether, 9.95 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR (CD_2Cl_2): δ = 0.01 (6H), 0.84 (9H), 1.07 (3H), 1.18 (3H), 1.2-1.7 (6H), 2.38 (1H), 3.57 (2H), 4.05 (2H) ppm.

Example 1r

(2S)-2-Methyl-6-(tert-butyldimethylsilyloxy)-hexan-1-ol

To a solution of 9.94 g of the ester prepared in Example 1q, in 130 mL of toluene, 63 mL of a 1.2 M solution of diisobutylaluminum hydride in toluene are added at -40°C under nitrogen and the mixture is stirred for 1 hour at this temperature. Then, carefully, 15 mL of isopropanol and after 10 minutes 30 mL of water are added, allowing the mixture to come to 22°C, and then the mixture is stirred at this temperature for 2 hours. The precipitate is filtered off, washed thoroughly with ethyl acetate and the filtrate is evaporated in vacuum. The residue thus obtained is purified by chromatography on silica gel. Using hexane/0-30% ether, 7.9 g of the compound in the title are obtained as a colorless oil. $[\alpha]_D$ -8.1° (c = 9.07, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 0.07 (3H), 0.89 (9H), 0.91 (3H), 1.0-1.7 (7H), 3.48 (2H), 3.52 (2H) ppm.

Example 1s

(2S)-2-Methyl-6-(tert-butyldimethylsilyloxy)-1-(tetrahydro-2H-pyran-2-yloxy)-hexane

To 6.4 g of the alcohol prepared according to Example 1r in 26 mL of methylene chloride, 3.52 mL of dihydropyrane are added at 0°C under argon, followed by 49 mg of p-toluene-sulfonic acid monohydrate. After 1.5 hours of stirring at 0°C, 10 mL of saturated sodium hydrogen carbonate solution are added, followed by dilution with ether. The organic phase is washed twice with half-saturated sodium chloride solution and dried over sodium sulfate. After filtration, it is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-5% ether, 4.75 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.05 (6H), 0.89 (9H), 0.92 (3H), 1.0-1.9 (13H), 3.19 (1H), 3.50 (1H), 3.55-3.65 (3H), 4.87 (1H), 4.57 (1H) ppm.

Example 1t

(5S)-5-Methyl-6-(tetrahydro-2H-pyran-2-yloxy)-hexan-1-ol

To a solution of 4.7 g of the THP ether prepared according to Example 1s, in 170 mL of tetrahydrofuran, 13.5 g of tetrabutylammonium fluoride trihydrate are added under nitrogen, followed by stirring for 3 hours. Then the reaction mixture is diluted with 800 mL of ether and is washed three times using 20 mL of half-saturated sodium chloride solution each time followed by drying over sodium sulfate. After filtration, the mixture is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-50% ethyl acetate, 2.88 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR (CD_2Cl_2): δ = 0.90/0.92 (3H), 1.1-1.9 (13H), 3.18 (1H), 3.40-3.65 (4H), 3.82 (1H), 4.53 (1H) ppm.

Example 1u

(2S)-6-Iodo-2-methyl-1-(tetrahydro-2H-pyran-2-yloxy)-hexane

To a solution of 13.4 g of triphenylphosphine and 3.47 g of imidazole in 200 mL of methylene chloride, 12.9 g of iodine are added. Then, the alcohol prepared in Example 1t in 50 mL of methylene chloride is added dropwise at 22°C, followed by stirring for 30

minutes. The mixture is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/5% ether, 10.2 g of the compound in the title are obtained as a slightly yellow-colored oil.

^{1}H-NMR ($CDCl_3$): δ = 0.94/0.95 (3H), 1.0-1.9 (13H), 3.1-3.3 (3H), 3.4-3.7 (2H), 3.85 (1H), 4.57 (1H) ppm.

Example 1v

(5S)-5-Methyl-6-(tetrahydro-2H-pyran-2-yloxy)-hex-1-yl-triphenylphosphoniumiodide

A mixture of 10.2 g of the iodide prepared above, 40.9 g of triphenylphosphine and 12.1 g of N-ethyldiisopropylamine is stirred at 80°C for 6 hours. After cooling, it is dissolved in 30 mL of methylene chloride and 500 mL of ether are added. The mixture is stirred for 10 minutes and then decanted. This is repeated another four times. The residue thus obtained is dissolved in anhydrous tetrahydrofuran, toluene is added, followed by evaporation in vacuum. Thus, 17.1 g of the compound in the title is obtained as a solid foam.

^{1}H-NMR ($CDCl_3$): δ = 0.85/0.86 (3H), 1.10 (1H), 1.7-1.9 (13H), 3.13 (1H), 3.40-3.55 (2H), 3.64 (1H), 3.79 (1H), 4.49 (1H), 7.6-7.9 (15H) ppm.

Example 1w

(*S*)-Dihydro-3-hydroxy-2(3*H*)-furanone

10 g of L-(-)-malic acid are stirred in 45 mL of trifluoroacetic acid anhydride for 2 hours at 25°C. Then the mixture is evaporated in vacuum, 7 mL of methanol are added to the residue and stirring is continued for 12 hours. This is followed by evaporation in vacuum. The obtained residue is dissolved in 150 mL of absolute tetrahydrofuran. The mixture is cooled to 0°C and 150 mL of borane/tetrahydrofuran complex is added, followed by stirring for 2.5 hours at 0°C. Then 150 mL of methanol are added. Stirring is continued for 1 hour at room temperature and then the mixture is evaporated in vacuum. The obtained crude product is dissolved in 80 mL of toluene. Then 5 g of Dowex® (activated, acid) are added and the mixture is boiled for one hour under reflux. The Dowex® is filtered off and the filtrate is evaporated in vacuum. The obtained crude product (7.61 g) is used in the next step without purification.

Example 1x

(*S*)-Dihydro-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2(3*H*)-furanone

To a solution of 7.61 g of the substance described in Example 1w and 10 g of imidazole in 100 mL of *N,N*-dimethylformamide, 24 mL of tert-butyldiphenylsilyl chloride are added. Stirring is continued for two hours at 25°C and then the reaction mixture is poured into ice-cold saturated sodium hydrogen carbonate solution. It is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 13.4 g of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.72 (2H), 7.70 (2H), 7.40-7.50 (6H), 4.30-4.42 (2H), 4.01 (1H), 2.10-2.30 (2H), 1.11 (9H) ppm.

Example 1y

(2RS,3*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]tetrahydro-2-furanol

To a solution of 13.4 g of the substance described in Example 1x in 150 mL of absolute tetrahydrofuran, 80 mL of a 1 molar solution of diisobutylaluminum hydride in hexane are added at -78°C. Stirring is continued for 45 minutes at -78°C, followed by quenching with water. The mixture is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. Thus, 13.46 g of the compound in the title are obtained, which is used without purification in the next step.

Example 1z

(2RS,3*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1,4-pentanediol

To 20 mL of a 3 molar solution of methylmagnesium chloride in tetrahydrofuran, a solution of 13.46 g of the substance described in Example 1y in 150 mL of absolute tetrahydrofuran are added dropwise at 0°C. Stirring is continued at 0°C for one hour and then the mixture is poured into saturated aqueous ammonium chloride solution. It is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude

product on silica gel with a mixture of hexane/ethyl acetate, 11.42 g of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.65-7.75 (4H), 7.40-7.55 (6H), 5.20 (1H), 4.30 (2H), 3.70 (1H), 1.80 (2H), 1.05 (9H) ppm.

Example 1aa

(2RS,3*S*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]-oxy]-2-pentanol

To a solution of 11.42 g of the substance described in Example 1z and 3.25 g of 1*H*-imidazole in 120 mL of *N,N*-dimethylformamide, 4.9 g of *tert*-butyldimethylsilyl chloride are added. Stirring is continued for 2 hours at 25°C and then the reaction mixture is poured into ice-cold saturated sodium hydrogen carbonate solution. This is followed by extraction with ethyl acetate, and then the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 10.64 g of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.60-7.70 (4H), 7.30-7.45 (6H), 3.70-3.80 (2H), 3.40 (1H), 3.00 (1H), 1.80 (1H), 1.60 (1H), 1.05-1.12 (12H), 0.82 (9H), 0.02 (6H) ppm.

Example 1ab

(3*S*)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-pentanone

To 7.37 mL of oxalyl chloride in 80 mL of dichloromethane, 13 mL of dimethylsulfoxide are added at -78°C. Stirring is continued for 3 minutes and then 10.46 g of the substance described in Example 1aa in 100 mL of dichloromethane are added. After another 15 minutes of stirring time, 52 mL of triethylamine are added dropwise. Then, the mixture is allowed to warm up to 0°C. After that, the reaction mixture is poured into saturated sodium hydrogen carbonate solution. It is extracted with dichloromethane, and then the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and

evaporated in vacuum. After column chromatography of the crude product on silica gel with a mixture of hexane/ethyl acetate, 9.3 g of the compound in the title are obtained.

^{1}H-NMR ($CDCl_3$): δ = 7.60-7.70 (4H), 7.32-7.50 (6H), 4.25 (1H), 3.72 (1H), 3.58 (1H), 2.05 (3H), 1.90 (1H), 1.75 (1H), 1.13 (9H), 0.89 (9H), 0.01 (6H) ppm.

Example 1 ac

(E,3S)-1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene

The solution of 6.82 g of diethyl(2-methylthiazol-4-yl)methane phosphonate in 300 mL of anhydrous tetrahydrofuran, is cooled in a dry argon atmosphere to -5°C, followed by the addition of 16.2 mL of a 1.6 molar solution of n-butyllithium in n-hexane. The mixture is allowed to warm up to 23°C and is stirred for 2 hours. Then it is cooled to -78°C, the solution of 6.44 g (13.68 mmole) of the compound prepared in Example 1ab in 150 mL of tetrahydrofuran are added dropwise, the mixture is allowed to warm up to 23°C and is stirred for 16 hours. It is poured into saturated ammonium chloride solution, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 6.46 g (11.4 mmole, 83%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.04 (6H), 0.83 (9H), 1.10 (9H), 1.79 (1H), 1.90 (1H), 1.97 (3H), 2.51 (3H), 3.51 (2H), 4.38 (1H), 6.22 (1H), 6.74 (1H), 7.23-7.47 (6H), 7.63 (2H), 7.70 (2H) ppm.

Example 1ad

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol

The solution of 4.79 g (8.46 mmole) of the compound, prepared according to Example 1ac in 48 mL of tetrahydrofuran, is treated with 48 mL of a 65:35:10 mixture of glacial acetic acid/water/tetrahydrofuran and stirred for 2.5 days at 23°C. It is poured into saturated sodium carbonate solution, extracted several times with ethyl acetate, the combined organic

extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. Thus, 3.42 g (7.57 mmole, 90%) of the compound in the title are isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.10 (9H), 1.53 (1H), 1.81 (2H), 1.96 (3H), 2.71 (3H), 3.59 (2H), 4.41 (1H), 6.38 (1H), 6.78 (1H), 7.26-7.49 (6H), 7.65 (2H), 7.72 (2H) ppm.

Example 1ae

(E,3S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-enal

To 1.55 mL of oxalyl chloride in 14.4 mL of methylene chloride, 2.73 mL of dimethylsulfoxide in 11.5 mL of methylene chloride are added dropwise at -70°C. Stirring is continued for 10 minutes and then 6.0 g of the alcohol described in Example 1ad in 11.5 mL of methylene chloride are added. After another 2 hours of stirring, 5.55 mL of triethylamine are added dropwise. Then the mixture is allowed to warm up to -40°C over the course of 1 hour and the reaction mixture is poured into 30 mL of water. The mixture is extracted twice with methylene chloride, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. The crude product thus obtained is used in the next step without further purification.

^{1}H-NMR ($CDCl_3$): δ = 1.09 (9H), 2.01 (3H), 2.51 (1H), 2.66 (1H), 2.72 (3H), 4.69 (1H), 6.43 (1H), 6.81 (1H), 7.3-7.8 (10H), 9.63 (1H) ppm.

Example 1af

(E,4S,2RS)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-5-methyl-6-(2-methylthiazol-4-yl)-hex-5-en-2-ol

To a solution of 5.9 g of the aldehyde prepared above, in 83 mL of tetrahydrofuran, 6.94 mL of a 3 molar methylmagnesium chloride solution in tetrahydrofuran are added dropwise at -10°C under nitrogen. After stirring for 30 minutes at -10°C, the reaction mixture is added to saturated ammonium chloride solution and extracted three times with ether. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. The crude product thus obtained is purified by

chromatography on silica gel. With hexane/0-80% ethyl acetate, 5.3 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.00-1.15 (12H), 1.55-1.90 (2H), 1.90/2.04 (3H), 2.69/2.72 (3H), 3.90 (1H), 4.40/4.48 (1H), 6.23/6.51 (1H), 6.69/6.80 (1H), 7.20-7.50 (6H), 7.60-7.80 (4H) ppm.

Example 1ag

(E,4S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-5-methyl-6-(2-methylthiazol-4-yl)-hex-5-en-2-one

To a solution of 5.25 g of the alcohol described above in 113 mL of acetone, 22.5 mL of Jones reagent are added dropwise at -40°C under vigorous stirring. The reaction mixture is allowed to warm up to -10°C in one hour and then 0.5 mL of isopropanol are added and stirring is continued for another 15 minutes. Now it is diluted with ether, washed four times with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-60% ethyl acetate, 4.01 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.07 (9H), 1.94 (3H), 2.00 (3H), 2.59 (1H), 2.70 (3H), 2.74 (1H), 4.73 (1H), 6.29 (1H), 6.75 (1H), 7.25-7.50 (6H), 7.60-7.75 (4H) ppm.

Example 1ah

(1E,5E/Z,3S,10S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2,5,10-trimethyl-1-(2-methyl-thiazol-4-yl)-11-(tetrahydro-2H-pyran-2-yloxy)-undec-1,5-diene

To a solution of 7.24 g of the phosphonium salt described in Example 1v, in 80 mL of tetrahydrofuran, 11.5 mL of a 1 molar solution of sodium bis(trimethylsilylamide) in tetrahydrofuran are added at 0°C under argon and then the mixture is stirred for 30 minutes at 22°C. Then, at -40°C, 2.61 g of the ketone prepared in Example 1ag in 8 mL of tetrahydrofuran are added and the mixture is stirred for 45 minutes at this temperature. The reaction mixture is introduced into saturated ammonium chloride solution and is extracted four times with ether. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum after filtration. The

residue thus obtained was purified with those from two other batches, in which a total of 3.57 g of the ketones from Example 1 ag were reacted, using chromatography on silica gel. With hexane/0-70% ether, 3.7 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.80-0.92 (3H), 0.92-1.95 (13H), 1.07 (9H), 1.30/1.44 (3H), 1.98/1.99 (3H), 2.15-2.40 (2H), 2.70 (3H), 3.08/3.18 (1H), 3.47-3.62 (2H), 3.85 (1H), 4.27 (1H), 4.55 (1H), 5.05 (1H), 6.19 (1H), 6.78 (1H), 7.24-7.48 (6H), 7.57-7.78 (4H) ppm.

Example 1ai

(6E/Z,10E,2S,9S)-9-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2,7,10-trimethyl-11-(2-methylthiazol-4-yl)-undec-6,10-dien-1-ol

To a solution of 4.0 g of the compound prepared in Example 1ah, in 21 mL of ethanol, 156 mg of pyridinium-p-toluenesulfonate are added and the mixture is stirred under argon for 24 hours at 50°C. Then it is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-60% ethyl acetate, 2.59 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.82/0.85 (3H), 0.91 (2H), 1.08 (9H), 1.05-1.90 (5H), 1.38/1.45 (3H), 2.00 (3H), 2.20-2.40 (2H), 2.70 (3H), 3.30-3.48 (2H), 4.26 (1H), 4.98/5.05 (1H), 6.15/6.18 (1H), 6.79 (1H), 7.20-7.50 (6H), 7.60-7.76 (4H) ppm.

Example 1ak

(6E/Z,10E,2S,9S)-9-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2,7,10-trimethyl-11-(2-methylthiazol-4-yl)-undec-6,10-dienal

To 0.416 mL of oxalyl chloride in 3.5 mL of methylene chloride, 0.729 mL of dimethylsulfoxide in 3.0 mL of methylene chloride are added dropwise at -70°C. The mixture is stirred for 10 minutes and then 2.0 g of the alcohol prepared above in 3.0 mL of methylene chloride are added. After another 2 hours of stirring, 1.49 mL of triethylamine are added dropwise. The mixture is allowed to warm up to -40°C within one hour and is introduced into 15 mL of water. It is extracted twice with methylene chloride, the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum. The crude product thus obtained (1.96 g) is used in the next step without further purification.

^{1}H-NMR ($CDCl_3$): δ = 0.97/1.01 (3H), 1.07 (9H), 1.0-2.1 (6H), 1.45/1.55 (3H), 2.00/2.01 (3H), 2.10-2.48 (3H), 2.69 (3H), 4.25/4.27 (1H), 5.01/5.03 (1H), 6.16/6.17 (1H), 6.79 (1H), 7.25-7.50 (6H), 7.58-7.77 (4H), 9.49/9.54 (1H) ppm.

Example 1al

(4S(4R,5S,6S,11E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-15-(2-methyl-4-thiazolyl)-3-oxo-5-hydroxy-2,4,6,11,14-pentamethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane (A) and

(4S(4R,5R,6S,11E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-15-(2-methyl-4-thiazolyl)-3-oxo-5-hydroxy-2,4,6,11,14-pentamethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane (B)

To a solution of 0.62 mL of diisopropylamine in 3 mL of tetrahydrofuran, 1.92 mL of a 2.4 molar solution of butyllithium in hexane are added at -30°C under argon. After 15 minutes of stirring, the mixture is cooled to -70°C and a solution of 857 mg of the compound prepared according to Example 1l in 3 mL of tetrahydrofuran is added dropwise. After one hour of stirring, 500 mg of the aldehyde prepared in Example 1ak in 3 mL of tetrahydrofuran are added dropwise. After 1.5 hours of stirring at this temperature, the reaction mixture is added to saturated ammonium chloride solution and extracted several times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride, dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-50% ether, 1.62 g of the compound in the title (A) are obtained as a colorless oil and 0.12 g of the diastereomeric compound B are obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.75/0.79 (3H), 1.00/1.01 (3H), 1.05 (9H), 1.09/1.10 (3H), 1.20 (3H), 1.30/1.43 (3H), 1.35 (3H), 1.43(3H), 0.80-1.95 (10H), 1.96/1.99 (3H), 2.03-2.40 (2H), 2.70 (3H), 3.18-3.40 (2H), 3.80-4.09 (3H), 4.27 (1H), 5.06 (1H), 6.18 (1H), 6.79 (1H), 7.22-7.48 (6H), 7.58-7.77 (4H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = 0.80-2.80 (18H), 1.02 (3H), 1.08 (12H), 1.28 (3H), 1.33 (3H), 1.41/1.42 (3H), 1.97/1.98 (3H), 2.71 (3H), 3.13-3.57 (2H), 3.75-4.15 (3H), 4.26 (1H), 5.03 (1H), 6.18 (1H), 6.78 (1H), 7.22-7.50 (6H), 7.53-7.70 (4H) ppm.

Example 1am

(4S(4R,5S,6S,11E/Z,13S,14E))-4-(13-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,4,6,11,14-pentamethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

To a solution of the compound in title A prepared above in 30 mL of methylene chloride, 200 mg of p-toluenesulfonic acid monohydrate and 3.03 mL of dihydropyran are added, followed by stirring for 3 days at 22°C. Then, the reaction mixture is poured into saturated sodium hydrogen carbonate solution and extracted with methylene chloride. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-40% ethyl acetate, 1.53 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.8-2.55 (37H), 1.06 (9H), 1.96/1.98 (3H), 2.69 (3H), 3.10-4.15 (8H), 4.26 (1H), 4.40-4.63 (1H), 5.05 (1H), 6.17 (1H), 6.78 (1H), 7.21-7.48 (6H), 7.55-7.74 (4H) ppm.

Example 1an

(4S(4R,5S,6S,11E/Z,13S,14E))-4-(13-Hydroxy-15-(2-methyl-4-thiazolyl)-3-oxo-5-(tetrahydropyran-2-yloxy)-2,4,6,11,14-pentamethyl-pentadeca-10,14-dien-2-yl)-2,2-dimethyl-[1,3]dioxane

To a solution of the compound prepared above, in 50 mL of tetrahydrofuran, 5.34 mL of a 1 molar solution of tetrabutylammonium fluoride in tetrahydrofuran are added and the mixture is first stirred for 12 hours at 22°C and then for 4 hours at 50°C. Then the reaction mixture is poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase is dried over sodium sulfate and is evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-80% ethyl acetate, 851 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.80-2.60 (39H), 2.07 (3H), 2.73 (3H), 3.28 (1H), 3.45 (1H), 3.60-4.33 (6H), 4.43-4.61 (1H), 5.25-5.43 (1H), 6.60 (1H), 6.95 (1H) ppm.

Example 1ao

(3S,6R,7S,8S,12E/Z,15S,16E)-17-(2-Methyl-4-thiazolyl)-5-oxo-4,4,6,8,13,16-hexamethyl-heptadeca-12,16-dien-1,3,7,15-tetraol

To a solution of 725 mg of the alcohol prepared above, in 33 mL of ethanol, 445 mg of p-toluenesulfonic acid monohydrate are added and the mixture is stirred for 3.5 hours under nitrogen at 22°C. Then the reaction mixture is poured into saturated sodium hydrogen carbonate solution and extracted with methylene chloride. The organic phase is dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-100% ethyl acetate/0-10% methanol, 505 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.84/0.87 (3H), 1.07 (3H), 1.13 (3H), 1.23 (3H), 1.68/1.77 (3H), 1.00-1.85 (10H), 2.06 (3H), 2.08-2.6 (3H), 2.72 (3H), 3.20-3.51 (4H), 3.89 (2H), 4.05 (1H), 4.23/4.29 (1H), 5.30/5.40 (1H), 6.61 (1H), 6.96/6.97 (1H) ppm.

Example 1ap

(3S,6R,7S,8S,12E/Z,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13,16-hexamethyl-1,3,7,15-tetrakis-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

To a solution of 490 mg of the tetraol prepared above, in 30 mL of methylene chloride, 4 mL of 2,6-lutidine are added, followed by dropwise addition of 3.9 mL of trifluoromethane-sulfonic acid tert-butyldimethylsilyl ester at -70°C under argon, and by stirring for 24 hours at -70°C. Then the reaction mixture is poured into saturated sodium hydrogen carbonate solution and extracted with methylene chloride. The organic phase is dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-50% ethyl acetate, 742 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.15 (24H), 0.90 (39H), 0.95-1.75 (9H), 1.05 (3H), 1.06 (3H), 1.22 (3H), 1.53/1.62 (3H), 2.00/2.02 (3H), 2.21 (2H), 2.71 (3H), 3.15 (1H), 3.58 (1H), 3.67 (1H), 3.77 (1H), 3.90 (1H), 4.23 (1H), 5.18 (1H), 6.49 (1H), 6.92/6.93 (1H) ppm.

Example 1aq

(3S,6R,7S,8S,12E/Z,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13-16-hexamethyl-1-hydroxy-3,7,15-tris-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-heptadeca-12,16-dien-5-one

To a solution of 735 mg of the silyl ether prepared above in a mixture of 8 mL of dichloromethane and 8 mL of methanol, 179 mg of camphor-10-sulfonic acid are added at 0°C under argon. The mixture is allowed to warm up to 22°C and is stirred for another 1.5 hours. Then 0.6 mL of triethylamine are added, the mixture is poured into a saturated sodium hydrogen carbonate solution and is extracted several times with dichloromethane. The organic phase is dried over sodium sulfate and is evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-20% ethyl acetate, 527 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.17 (18H), 0.93 (30H), 1.09 (9H), 0.90-1.54 (8H), 1.66/1.73 (3H), 1.93 (2H), 2.00/2.03 (3H), 2.20 (2H), 2.73 (3H), 3.15 (1H), 3.67 (2H), 3.81 (1H), 4.10 (1H), 4.23 (1H), 5.20 (1H), 6.47 (1H), 6.92/6.94 (1H) ppm.

Example 1ar

(3S,6R,7S,8S,12E/Z,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13,16-hexamethyl-3,7,15-tris-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-5-oxo-heptadeca-12,16-dienal

To a solution of 520 mg of the alcohol prepared above, in 30 mL of methylene chloride, 1.28 g of Collins reagent are added at 0°C under argon and the mixture is stirred for 15 minutes at 0°C. Then Celite is added and the mixture is diluted with ether. It is filtered through the Celite, washed thoroughly with ether and the filtrate is evaporated in vacuum. The compound in the title thus obtained (463 mg) is used in the next step as a pale-yellow oil without further purification.

^{1}H-NMR ($CDCl_3$): δ = 0.0-0.17 (18H), 0.91 (30H), 1.05 (3H), 1.10 (3H), 1.27 (3H), 1.65/1.72 (3H), 1.00-1.62 (8H), 2.00/2.03 (3H), 2.21 (2H), 2.30-2.58 (3H), 2.72 (3H), 3.14 (1H), 3.79 (1H), 4.23 (1H), 5.20 (1H), 6.47 (1H), 6.92/6.94 (1H) ppm.

Example 1as

(3S,6R,7S,8S,12Z,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13,16-hexamethyl-3,7,15-tris-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-5-oxo-heptadeca-12,16-dienoic acid (A) and (3S,6R,7S,8S,12E,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13,16-hexamethyl-3,7,15-tris-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-5-oxo-heptadeca-12,16-dienoic acid (B)

To a solution of 530 mg of the aldehyde prepared above, in 19.5 mL of acetone, 1.5 mL of a standardized 8 N chromsulfuric acid solution are added at -30°C and the mixture is stirred for 45 minutes. Then it is poured into a mixture of water and diethyl ether and the organic phase is washed twice with saturated sodium chloride solution. The organic phase is dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel, performed twice. With hexane/0-90% ethyl acetate, 162 mg of the compound A in the title as nonpolar component and 171 mg of compound B in the title as the polar component are obtained as colorless oils.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.00-0.18 (18H), 0.88 (30H), 0.90-1.68 (7H), 1.09 (3H), 1.17 (3H), 1.20 (3H), 1.75 (3H), 1.98 (3H), 2.00-2.50 (4H), 2.72 (3H), 3.16 (1H), 3.73 (1H), 4.33 (1H), 4.43 (1H), 5.23 (1H), 6.72 (1H), 6.97 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = 0.00-0.17 (18H), 0.90 (30H), 0.90-1.45 (7H), 1.07 (3H), 1.13 (3H), 1.23 (3H), 1.63 (3H), 1.97 (3H), 1.85-2.58 (4H), 2.51 (3H), 3.17 (1H), 3.80 (1H), 4.21 (1H), 4.39 (1H), 5.18 (1H), 6.46 (1H), 6.92 (1H) ppm.

Example 1at

(3S,6R,7S,8S,12E,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13,16-hexamethyl-3,7-bis-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-5-oxo-heptadeca-12,16-dienoic acid

To a solution of 50 mg of the compound B in the title prepared in Example 1as, in 1.5 mL of tetrahydrofuran, 0.59 mL of a 1 molar solution of tetrabutylammonium fluoride are added at 22°C under argon, followed by stirring for 16 hours. Then the reaction mixture is poured into ice cold saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic phases are washed once with 1 N hydrochloric acid and once with saturated sodium chloride solution. The organic phase is dried over sodium sulfate and evaporated in vacuum after filtration. The residue thus obtained is purified by chromatography on silica gel. With hexane/0-80% ethyl acetate, 42 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.15 (12H), 0.91 (21H), 1.07 (3H), 1.13 (3H), 1.23 (3H), 0.80-1.50 (9H), 1.69 (3H), 2.03 (3H), 2.11-2.58 (4H), 2.73 (3H), 3.15 (1H), 3.80 (1H), 4.24 (1H), 4.41 (1H), 5.31 (1H), 6.53 (1H), 6.95 (1H) ppm.

Example 1 au

(4S,7R,8S,9S,13E,16S(E))-4,8-Bis-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

To a solution of 118 mg of the acid prepared above, in 6 mL of tetrahydrofuran, 75 μL of triethylamine, 50 μL 2,4,6-trichlorobenzoyl chloride are added under argon and the mixture is stirred for 15 minutes. This solution is added over a period of 3 hours to a solution of 195 mg of 4-dimethylaminopyridine in 90 mL of toluene and then the mixture is stirred for another 15 minutes at 23°C. It is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel.. With hexane/0-40% ethyl acetate, 87 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.17 (12H), 0.87 (9H), 0.93 (9H), 0.96 (3H), 1.12 (3H), 1.14 (3H), 1.21 (3H), 1.63 (3H), 2.14 (3H), 1.00-2.37 (10H), 2.49 (1H), 2.62 (1H), 2.73 (1H), 2.82 (1H), 3.05 (1H), 3.92 (1H), 4.20 (1H), 5.31 (1H), 5.37 (1H), 6.59 (1H), 6.95 (1H) ppm.

Example 1

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

To a solution of 45 mg of the lactone prepared above in 1.5 mL of methylene chloride, 348 μL of a 20% solution of trifluoroacetic acid in methylene chloride are added at -10°C under argon. The mixture is allowed to warm up to 0°C and is stirred for 5 hours at this temperature. The reaction mixture is evaporated in vacuum and the residue thus obtained is purified by chromatography on silica gel. With hexane/0-80% ethyl acetate, 22.4 g of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$: δ = 0.99 (3H), 1.08 (3H), 1.20 (3H), 1.31 (3H), 1.64 (3H), 1.05-1.75 (5H), 1.90 (1H), 2.01 (3H), 2.21 (2H), 2.34 (1H), 2.49-2.52 (3H), 2.72 (3H), 3.10 (1H), 3.22 (1H), 3.77 (1H), 4.02 (1H), 5.31 (1H), 5.52 (1H), 6.58 (1H), 6.98 (1H) ppm.

Example 2

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione(A) and (1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione(B)

To a solution of 20 mg of the title compound prepared in Example 1, in 0.4 mL of acetonitrile, 233 μL of a 0.1037 molar disodium EDTA salt solution and 389 μL of 1,1,1-trifluoroacetone are added at 0°C under argon. Then a mixture of 47.6 mg of oxone and 27.3 mg of sodium hydrogen carbonate is added and the mixture is stirred for 2.5 hours at 0°C. Then sodium thiosulfate solution is added and the mixture is extracted several times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in vacuum after filtration. A second batch of the same size yields another batch of the crude product. The combined crude products thus obtained are purified by preparative thick-layer chromatography with hexane/50% ethyl acetate. The actual separation of the compounds A and B in the title is done by HPLC separation (Chiralpak AD 10 μ; hexane:ethanol 85:15). In this way, 6.7 mg of compound A in the title and 16.2 mg of compound B in the title are obtained as colorless oils.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.99 (3H), 1.05 (3H), 1.16 (3H), 1.43 (3H), 1.45 (3H), 1.05-1.72 (8H), 2.00 (2H), 2.09 (3H), 2.44 (2H), 2.72 (3H), 2.89 (1H), 3.50 (1H), 3.83 (1H), 4.14 (1H), 4.50 (1H), 5.62 (1H), 6.57 (1H), 6.98 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = 1.03 (3H), 1.13 (3H), 1.23 (3H), 1.34 (3H), 1.36 (3H), 1.07-1.72 (7H), 1.70 (1H), 2.08 (3H), 2.22 (2H), 2.50 (1H), 2.60 (1H), 2.72 (3H), 2.93 (1H), 3.25 (1H), 3.57 (1H), 3.82 (1H), 4.05 (1H), 5.44 (1H), 6.66 (1H), 6.98 (1H) ppm.

Example 3
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

Example 3a
(3S,6R,7S,8S,12Z,15S,16E)-17-(2-Methyl-4-thiazolyl)-4,4,6,8,13,16-hexamethyl-3,7-bis-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-15-hydroxy-5-oxo-heptadeca-12,16-dienoic acid
Compound A in the title, prepared according to Example 1r, 150 mg, is reacted analogously to Example 1s. Thus, 81 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.16 (12H), 0.90 (21H), 1.08 (3H), 1.17 (3H), 1.18 (3H), 0.80-2.28 (8H), 1.78 (3H), 2.03 (3H), 2.30-2.55 (4H), 2.73 (3H), 3.14 (1H), 3.78 (1H), 4.28 (1H), 4.42 (1H), 5.38 (1H), 6.78 (1H), 6.97 (1H) ppm.

Example 3b
(4S,7R,8S,9S,13Z,16S(E))-4,8-Bis-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione
The compound prepared above, 81 mg, is reacted in analogously to Example 1au. After column chromatography, 75 mg are obtained which are purified once more by preparative thick-layer chromatography with hexane/10% ethyl acetate. Thus, 58 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.00-0.17 (12H), 0.79-0.99 (24H), 1.09 (3H), 1.16 (3H), 1.72 (3H), 1.00-1.92 (8H), 2.12 (3H), 2.31 (2H), 2.68 (1H), 2.71 (1H), 2.88 (1H), 2.99 (2H), 3.89 (1H), 3.98 (1H), 5.06 (1H), 5.27 (1H), 6.59 (1H), 6.98 (1H) ppm.

Example 3 [sic, should be 3c]
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione
The compound prepared above, 27 mg, is reacted in analogy to Example 1. The purification is done by preparative thick-layer chromatography with hexane/20% ethyl acetate. Thus, 17.4 mg of the compound in the title are obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.11 (3H), 1.20 (3H), 1.35 (3H), 1.75 (3H), 1.10-2.05 (7H), 2.10 (3H), 2.20 (1H), 2.39 (1H), 2.51 (1H), 2.70 (3H), 2.83-3.01 (2H), 3.14 (1H), 3.80 (1H), 3.42 (1H), 4.20 (1H), 5.23 (1H), 5.40 (1H), 6.62 (1H), 6.98 (1H) ppm.

Example 4

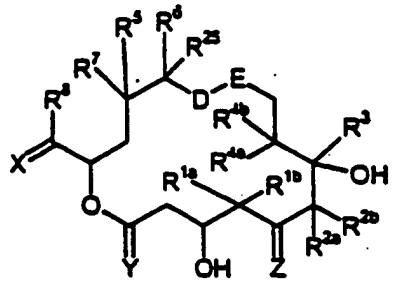
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione(A) and (1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione(B)

The compound prepared in Example 3, 15 mg, is reacted analogously to Example 2. The purification is done only by preparative thick-layer chromatography. Thus, 0.3 mg of compound A in the title and 11 mg of compound B in the title are obtained as colorless oils.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.94 (3H), 1.04 (3H), 1.10 (3H), 1.41 (3H), 1.43 (3H), 1.05-2.20 (7H), 2.12 (3H), 2.24-2.65 (4H), 2.73 (3H), 3.32 (1H), 3.40-3.82 (2H), 4.07 (1H), 5.80 (1H), 6.62 (1H), 6.98 (1H) ppm.
^{1}H-NMR ($CDCl_3$) of B: δ = 1.03 (3H), 1.15 (3H), 1.21 (3H), 1.36 (3H), 1.38 (3H), 1.10-1.97 (9H), 2.05 (3H), 2.09 (1H), 2.42 (1H), 2.53 (1H), 2.70 (3H), 2.72 (1H), 3.14 (1H), 3.67 (1H), 3.81 (1H), 4.12 (1H), 5.49 (1H), 6.56 (1H), 6.97 (1H) ppm.

Patent Claims

1. Epothilone derivatives having general formula I,



I,

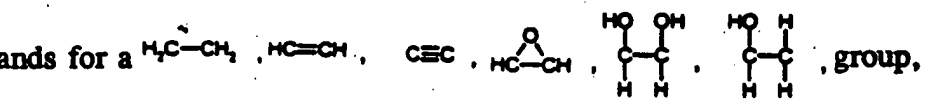
where

R^{1a}, R^{1b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for an -$(CH_2)_m$ group where m = 2, 3, 4 or 5,

R^{2a}, R^{2b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a -$(CH_2)_n$ group where n = 2, 3, 4 or 5,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^{4a}, R^{4b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for an -$(CH_2)_p$ group with p = 2, 3, 4 or 5,

D-E stands for a  , group,

R^5 is C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^6, R^7 each stands for a hydrogen atom, together for an additional bond or for an oxygen atom,

R^{25} is hydrogen, C_1-C_{10} alkyl, where the alkyl group optionally can be substituted by one or several halogen atoms and/or hydroxyl groups,

R^8 is hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, all of which can be substituted,

X is an oxygen atom, two alkoxy groups OR^9, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^{10} or a $CR^{11}R^{12}$ group, where

R^9 stands for a C_1-C_{20} alkyl group,

R^{10} stands for hydrogen or a protective group PG^1,

R^{11},R^{12} can be the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^{11} and R^{12} together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

Y is an oxygen atom or two hydrogen atoms,

Z is an oxygen atom or H/OR^{13},

where

R^{13} is a hydrogen atom or a protective group PG^2,

including all stereoisomers of these compounds and their mixtures.

2. Epothilone derivatives having general formula I according to Claim 1, where R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^{25} and R^7 all can have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

3. Epothilone derivatives of general formula I according to Claim 1, where R^5, R^6, R^{25}, R^7, R^8 and X can all have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

4. Epothilone derivatives having general formula I according to Claim 1, where Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^{25} and R^7 all can have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

5. Epothilone derivatives having general formula I according to Claim 1, where Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^5, R^6, R^{25}, R^7, R^8 and X can all have the meaning given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

6. Epothilone derivatives having general formula I according to Claim 1, where R^3, R^{4a}, R^{4b}, D-E, R^5, R^6, R^{25}, R^7, R^8 and X all can have the meanings given in general formula I and the rest of the molecule is identical with the naturally occurring epothilone A or B.

7. Epothilone derivatives having general formula I according to Claim 1, where R^5 stands for a methyl, ethyl or propyl group.

8. Epothilone derivatives having general formula I according to Claim 7, where R^6 and R^7 together stand for an additional bond.

9. Epothilone derivatives having general formula I according to Claim 7, where R^6 and R^7 together stand for an epoxy group.

10. Epothilone derivatives having general formula I according to Claim 1, where R^{25} stands for a hydrogen atom, a methyl, ethyl, propyl, hydroxymethyl, fluoromethyl or trifluoromethyl group.

11. Compounds having general formula I according to Claim 1, namely

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14,1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,14-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5-dimethylene-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,14-trimethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8-dimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8-dimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5-trimethylene-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7,9,14-trimethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8-trimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-8,8-trimethylene-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-methyl-4-oxazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9,dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7,14-diethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1,10-diethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1,10-diethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-14-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethen-yl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethen-yl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-oxazolyl)ethenyl)-1-oxa-5,5,7,9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethen-yl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-oxazolyl)ethen-yl)-1,8,8,10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,-9,14-pentamethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-1,8,8,-10,12-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,14-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,8,8,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

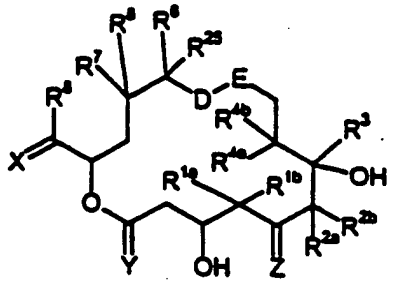
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-14-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-14-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione

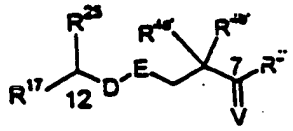
(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-1-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
and
(1R,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-1-propyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

12. Method for the preparation of the epothilone derivatives having general formula I according to Claim 1,



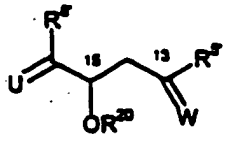
I,

where
the substituents have the meanings given in general formula I,
characterized by the fact
that a fragment of general formula B



B

where
$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and R^{25} have the meanings given already for R^3, R^{4a}, R^{4b} and R^{25}, and
R^{17} is a hydroxyl group, halogen, a protected hydroxyl group OPG^3, a phosphonium halide group $PPh_3^+Hal^-$ (Ph = phenyl, Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl), or a phosphine oxide group $P(O)Ph_2$ (Ph = phenyl),
is reacted with a fragment having general formula C



C

where

$R^{5'}$, $R^{8'}$ have the meaning already given in general formula I for R^5 and R^8 and

R^{20} stands for a hydrogen atom or a protective group PG^5

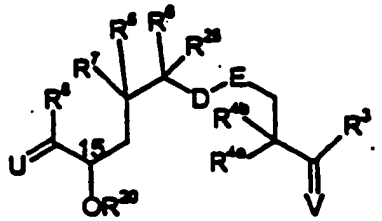
U stands for oxygen atom, two alkoxy groups OR^9, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^{10} or a $CR^{11}R^{12}$ group, where

- R^9 stands for a C_1-C_{20} alkyl group,
- R^{10} stands for a hydrogen or a protective group PG^6,
- R^{11}, R^{12} can be the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^{11} and R^{12} together with the methylene carbon atom stand for a 5- to 7-membered carbocyclic ring,

W is an oxygen atom, two alkoxy groups OR^{21}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched or H/OR^{22}, where

- R^{21} stands for a C_1-C_{20} alkyl group,
- R^{22} stands for hydrogen or a protective group PG^7,

to form a partial fragment having general formula BC

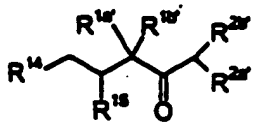


BC,

where

R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^{20}, D, E, U and V have the meanings already given,

and then this partial fragment BC is reacted with a fragment having general formula A



A,

where

$R^{1a'}$, $R^{1b'}$, $R^{2a'}$ and $R^{2b'}$ have the meanings already given for R^{1a}, R^{1b}, R^{2a} and R^{2b} and

R^{14} stands for CH_2OR^{14a}, CH_2-Hal, CHO, CO_2R^{14b}, COHal,

R^{15} stands for hydrogen, OR^{15a}, Hal, OSO_2R^{15b},

R^{14a}, R^{15a} stand for hydrogen, SO_2-alkyl, SO_2-aryl, SO_2-aralkyl or together for a $(CH_2)_o$ group or together for a $CR^{16a}R^{16b}$ group,

R^{14b}, R^{15b} stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7C_{20} aralkyl,

R^{16a}, R^{16b} are the same or different and stand for hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together for a $-(CH_2)_q$ group,

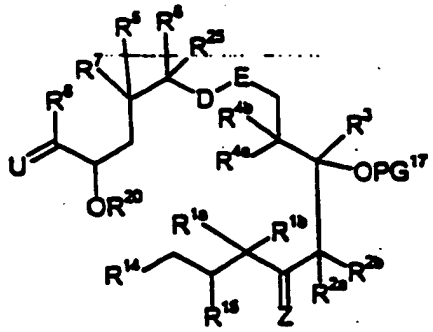
Hal is halogen,

o is 2 to 4,

q is 3 to 6,

including all stereoisomers as well as their mixtures as well as the free hydroxyl group in R^{14} and R^{15} can be etherified or esterified, the free carbonyl groups in A and R^{14} can be ketalized, converted into an enol ether or reduced, as well as the free acid groups in A can be converted to their salts with bases,

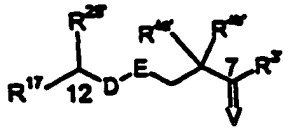
to form a partial fragment having general formula ABC



ABC,

where R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^8, R^{14}, R^{15}, D, E, U and Z have the meanings already given,
and then this partial fragment having general formula ABC is cyclized to an epothilone derivative of the general formula.

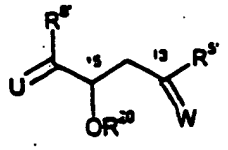
13. Intermediate products having general formula B



B

where
$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and $R^{25'}$ have the meanings already given for R^3, R^{4a}, R^{4b} and R^{25}, and
R^{17} stands for a hydroxyl group, halogen, a protected hydroxyl group OPG^3, a phosphonium halide group $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate group $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphine oxide group $P(O)Ph_2$ (Ph = phenyl).

14. Intermediate products having general formula C



C

where

$R^{5'}$, $R^{8'}$ have the meaning already given for R^5 and R^8 in general formula I and

R^{20} stands for a hydrogen atom or a protective group PG^5,

U stands for an oxygen atom, two alkoxy groups OR^9, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR^{10} or a $CR^{11}R^{12}$ group,

where

R^9 stands for a C_1-C_{20} alkyl group,

R^{10} stands for hydrogen or a protective group PG^6,

R^{11}, R^{12} are the same or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl group or R^{11} and R^{12} together with the methylene carbon atom can stand for a 5- to 7-membered carbocyclic ring,

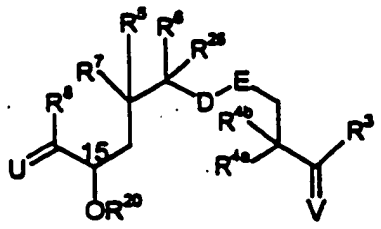
W is an oxygen atom, two alkoxy groups OR^{21}, a C_2-C_{10} alkylene-α,ω-dioxy group, which can be straight-chain or branched or H/OR^{22},

where

R^{21} stands for a C_1-C_{20} alkyl group,

R^{22} stands for hydrogen or a protective group PG^7.

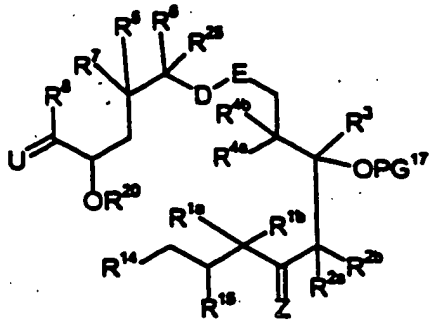
15. Intermediate products having general formula BC



BC,

where
R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^{20}, D, E, U and V have the meanings already given above.

16. Intermediate products of general formula ABC



ABC,

where R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^6, R^{25}, R^7, R^8, R^{14}, R^{15}, D, E, U and Z have the meanings already given above.

17. Pharmaceutical preparations, containing at least one compound having general formula I according to Claim 1, as well as a pharmaceutically compatible carrier.

18. Application of the compounds of general formula I according to Claim 1 for the production of drugs.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D313/00 C07D493/04 C07D417/06 C07D413/06 C07D405/06
C07F9/54 C07D277/24 A61K31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 25929 A (NOVARTIS-THE SCRIPPS RESEARCH INSTITUTE) 18 June 1998 (1998-06-18) page 40 -page 49; claims	1-13, 16-18
X	WO 97 19086 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG) 29 May 1997 (1997-05-29) page 1 -page 7; claims	1,12, 16-18

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 1999	03/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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